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European Patent Office  
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(11) **EP 1 439 393 A2**

(12) **EUROPEAN PATENT APPLICATION**

(43) Date of publication:  
21.07.2004 Bulletin 2004/30

(51) Int Cl.7: **G01N 33/574, G01N 33/53**

(21) Application number: **03257868.4**

(22) Date of filing: **15.12.2003**

(84) Designated Contracting States:  
**AT BE BG CH CY CZ DE DK EE ES FI FR GB GR  
HU IE IT LI LU MC NL PT RO SE SI SK TR**  
Designated Extension States:  
**AL LT LV MK**

(30) Priority: **13.12.2002 US 433554 P**  
**31.07.2003 US 491397 P**

(71) Applicants:  
• **Bayer Healthcare LLC**  
**Tarrytown, New York 10591-5097 (US)**  
• **MAYO FOUNDATION FOR MEDICAL  
EDUCATION AND RESEARCH**  
**Rochester, MN 55905 (US)**

(72) Inventors:  
• **Astle, Jon H.**  
**Taunton, MA 02780 (US)**  
• **Boardman, Lisa Allyn**  
**Rochester, MN 55902 (US)**  
• **Bugart, Lawrence J.**  
**Rochester, MN 55901 (US)**  
• **Burgess, Christopher C.**  
**Westwood, MA 02090 (US)**  
• **Catino, Theodore J.**  
**Attleboro, MA 02702 (US)**

- **Dwivedi, Poornima**  
**Alamo, CA 94507 (US)**
- **Huntress, Maryanne**  
**Attleboro, MA 02703 (US)**
- **Johnson, Karen Anne**  
**Action, MA 01720 (US)**
- **Lewis, Marcia E.**  
**Cohasset, MA 02025 (US)**
- **Maimonis, Peter J.**  
**Westwood, MA 02090 (US)**
- **Myerow, Susan H.**  
**Lexington, MA 02421 (US)**
- **Brown-Shimer, Sheryl Lynn Andrea**  
**Boston, MA 02118 (US)**
- **Thiagalingam, Arunthathi**  
**Lexington, MA 02420 (US)**
- **Thibodeau, Stephen N.**  
**Rochester, MN 55906 (US)**
- **Molino, Gary A.**  
**Norfolk, MA 02056 (US)**

(74) Representative: **Grant, Anne Rosemary**  
**Frank B. Dehn & Co.**  
**179 Queen Victoria Street**  
**London EC4V 4EL (GB)**

(54) **Detection methods using TIMP 1 for colon cancer diagnosis**

(57) The present invention relates to a method for detecting the presence of colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 $\alpha$  or TIMP1 nucleic acid or amino acid molecules in a clinical sample obtained from the patient, wherein Reg1 $\alpha$  or TIMP1 expression is indicative of the presence of colorectal cancer. The invention further relates to a method for detecting the presence of

colorectal cancer in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 $\alpha$  or TIMP1 nucleic acid or amino acid molecules in a clinical sample, in addition to detecting the presence of one or more additional colorectal cancer associated markers.

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### DETECTION METHODS USING TIMP1

Colorectal carcinoma is a malignant neoplastic disease. There is a high incidence of colorectal carcinoma in the Western world, particularly in the United States. Tumors of this type often metastasize through lymphatic and vascular channels. Many patients with colorectal carcinoma eventually die from this disease. In fact, it is estimated that 62,000 persons in the United States alone die of colorectal carcinoma annually.

However, if diagnosed early, colorectal cancer may be treated effectively by surgical removal of the cancerous tissue. Colorectal cancers originate in the colorectal epithelium and typically are not extensively vascularized (and therefore not invasive) during the early stages of development. Colorectal cancer is thought to result from the clonal expansion of a single mutant cell in the epithelial lining of the colon or rectum. The transition to a highly vascularized, invasive and ultimately metastatic cancer which spreads throughout the body commonly takes ten years or longer. If the cancer is detected prior to invasion, surgical removal of the cancerous tissue is an effective cure. However, colorectal cancer is often detected only upon manifestation of clinical symptoms, such as pain and black tarry stool. Generally, such symptoms are present only when the disease is well established, often after metastasis has occurred, and the prognosis for the patient is poor, even after surgical resection of the cancerous tissue. Early detection of colorectal cancer therefore is important in that detection may significantly reduce its morbidity.

Invasive diagnostic methods such as endoscopic examination allow for direct visual identification, removal, and biopsy of potentially cancerous growths such as polyps. Endoscopy is expensive, uncomfortable, inherently risky, and therefore not a practical tool for screening populations to identify those with colorectal cancer. Non-invasive analysis of stool samples for characteristics indicative of the presence of colorectal cancer or precancer is a preferred alternative for early diagnosis, but no known diagnostic method is available which reliably achieves this goal. A reliable, non-invasive, and accurate technique for diagnosing colorectal cancer at an early stage would help save many lives.

Ectopic expression of the pancreatic regenerating gene (RegI) has been identified previously in colorectal tumors, and suggested as a potential marker for colorectal cancer (Zenilman et al., (1997) *J. Gastrointest. Surg.*, 1: 194; Watanabe et al., (1990) *J. Biol. Chem.*, 265: 7432; Birse and Rosen, WO01/12781). At present, there is no reliable method known to those of skill in the art for the rapid and accurate detection of RegI $\alpha$  in the serum of colorectal

cancer patients (Satomura et al., (1995) *J. Gastroenterol.* 30: 643). There is thus a need in the art for a method of detecting, and/or monitoring colorectal cancer in a patient utilizing the expression of Reg1 $\alpha$  in serum.

5 The present invention provides a method of detecting, monitoring or determining the therapeutic response of colorectal cancer in an individual as well as compositions, and kits for performing the method. In its most general aspect, the method comprises: obtaining a clinical sample from the individual and detecting the presence of one or more of the nucleic acid sequences of SEQ ID Nos. 1, 3, or 5-71, or the amino acid sequences of SEQ ID Nos. 2, 4, or 72-138.

10 The invention also provides a method of detecting, monitoring or determining the therapeutic response of colorectal cancer in an individual as well as compositions, and kits for performing the method, which, in its preferred aspect, comprises: obtaining a clinical sample from the individual and detecting the presence of Reg1 $\alpha$  or TIMP1 in said sample, wherein the presence of Reg1 $\alpha$  or TIMP1 in the sample is indicative of the presence or stage of colorectal  
15 cancer in the individual.

In one embodiment, the step of detecting comprises: contacting said clinical sample with a ligand which is capable of binding to Reg1 $\alpha$  or TIMP1 under conditions which permit the ligand to bind to Reg1 $\alpha$  or TIMP1; and detecting the binding of the ligand to Reg1 $\alpha$  or TIMP1, wherein detection of binding is indicative of the presence of Reg1 $\alpha$  or TIMP1 in the sample.  
20 The polypeptide ligand may comprise, for example, an antibody, peptide, oligonucleotide, or other molecule that specifically binds Reg1 $\alpha$  or TIMP1. In a currently preferred embodiment, the clinical sample comprises serum.

The present invention further provides a method of detecting, monitoring, or determining the presence of colorectal cancer in an individual comprising: obtaining a clinical sample from  
25 said individual; and detecting the presence of Reg1 $\alpha$  or TIMP1 and at least one other colorectal cancer associated marker in the sample, wherein the presence of Reg1 $\alpha$  or TIMP1 and the at least one other colorectal cancer associated marker is indicative of colorectal cancer in the individual. The colorectal cancer associated marker may comprise, for example, one or more of the nucleic acid sequences of SEQ ID Nos 1, 3, or 5-71, or the amino acid sequences of SEQ ID Nos 2, 4, or  
30 72-138, or derivatives or homologs thereof having substantially the same binding specificity.

In a preferred embodiment, the above step of detecting comprises contacting a serum sample with a first ligand which is capable of binding to Reg1 $\alpha$  or TIMP1 and a second

ligand which is capable of binding to the colorectal cancer associated marker, under conditions which permit the first and second ligands to bind to Reg1 $\alpha$  or TIMP1 and the colorectal cancer associated marker, respectively; and detecting the binding of the first ligand to Reg1 $\alpha$  or TIMP1 and the second ligand to the colorectal cancer associated marker, wherein detection of binding is  
5 indicative of the presence of Reg1 $\alpha$  or TIMP1 and the colorectal cancer associated marker in said sample. The polypeptide ligand may comprise, for example, an antibody, peptide, oligonucleotide, or other molecule that specifically binds Reg1 $\alpha$  or TIMP1.

The present invention also provides a method of detecting, monitoring or determining the presence of colorectal cancer in an individual comprising: obtaining a clinical sample from an  
10 individual; and detecting the presence of a nucleic acid molecule which encodes Reg1 $\alpha$  or TIMP1 in said sample, wherein the presence of the nucleic acid molecule in the sample is indicative of colorectal cancer in the individual.

The invention still further provides a method of detecting, monitoring or determining the presence of colorectal cancer in an individual comprising: obtaining a clinical sample from an  
15 individual; and detecting the presence of a nucleic acid molecule which encodes Reg1 $\alpha$  or TIMP1 and at least one other nucleic acid molecule which encodes at least one other colorectal cancer associated marker in the sample, wherein the presence of the nucleic acid sequence encoding Reg1 $\alpha$  or TIMP1 and the nucleic acid sequence encoding the at least one other colorectal cancer associated marker is indicative of colorectal cancer in the individual. In a  
20 preferred embodiment, the colorectal cancer associated marker is one or more of the nucleic acid sequences of SEQ ID Nos 1, 3, or 5-71, or the amino acid sequences of SEQ ID Nos 2, 4, or 72-138, or derivatives or homologs thereof having substantially the same binding specificity.

Figure 1 shows the level of Reg1 $\alpha$  polypeptide present in serum obtained from normal control patients (n=35), patients diagnosed with inflammatory bowel disease (IBD; n=7), patients  
25 diagnosed with cirrhosis (n=7), and patients diagnosed with colorectal cancer (n=63).

Figure 2 shows the level of Reg1 $\alpha$  polypeptide measured in the colorectal cancer patient group (n=63) differentiated based on cancer severity. The degree of cancer has been established by Dukes'-type staging, and data from patients with Dukes'-type A, B, C, and D is shown.

Figure 3 shows a graphical representation of the plasma level of TIMP1 polypeptides,  
30 along with one or more other colorectal cancer associated markers obtained from patients with colorectal cancer.



The present invention is based, in part, on the discovery that the expression of the human islet regenerating protein, Reg1 $\alpha$ , is increased in patients with colorectal cancer, and as such is a valuable marker for the identification of colorectal cancer in humans. The present invention further provides for the early detection of colorectal cancer by detecting the presence of Reg1 $\alpha$  or TIMP1 (and optionally, one or more additional colorectal cancer associated markers) in a clinical sample from an individual. The invention provides further, the ability to monitor the recurrence of colorectal cancer in a patient wherein colorectal cancer has been previously detected, by monitoring the levels of Reg1 $\alpha$  or TIMP1 polypeptide or polynucleotide sequences present in a clinical sample from the patient, wherein an increase in Reg1 $\alpha$  or TIMP1 in the sample is indicative of the recurrence of colorectal cancer. The invention provides still further, the ability to monitor the decrease in colorectal cancer in response to a therapeutic agent, whereby the levels of Reg1 $\alpha$  or TIMP1 are measured in a clinical sample obtained from a patient who has received therapeutic treatment for colorectal cancer, wherein a decrease in the levels of Reg1 $\alpha$  or TIMP1 detected in the clinical sample from the patient is indicative of the efficacy of the therapeutic treatment. In any of the preceding embodiments, Reg1 $\alpha$  or TIMP1 polynucleotide or polypeptide expression levels are measured in concert with at least one additional colorectal cancer associated marker.

Accordingly, the present invention relates in part to novel methods for identifying cancer in an individual, particularly colorectal cancer, by screening for genes or gene products, which are over or underexpressed in cancer relative to the level of expression in normal tissue, such as colon tissue. Alternatively, the invention provides a method for the identification of cancer in an individual by screening for genes or gene products which are over- or underexpressed in colorectal cancer, and which are detectable in a clinical sample of an individual with colorectal cancer.

In a preferred embodiment, the present invention relates to methods useful for the detection of colorectal cancer in an individual, preferably a human patient by detecting serum levels of Reg1 $\alpha$  or TIMP1. The invention relates to methods for colorectal cancer detection that utilize either or both techniques of detecting the presence of the Reg1 $\alpha$  or TIMP1 gene or detecting the Reg1 $\alpha$  or TIMP1 encoded polypeptide product in the serum of an individual, or alternatively in a clinical sample from an individual.

The present invention further provides methods for the identification of colorectal cancer wherein cancer is detected by the identification of Reg1 $\alpha$  or TIMP1 expression in a patient

clinical sample, in combination with the expression in the same sample of at least one other colorectal cancer associated marker. This combination of Reg1 $\alpha$  or TIMP1 detection analysis, in concert with the detection of additional colon-cancer markers provides an efficient and reliable method for detecting the presence of colorectal cancer.

5           The methods described herein which specifically refer to the detection of Reg1 $\alpha$ , may equally be applied to the detection of TIMP1 by one of skill in the art, based on the disclosure of the present specification:

          As used herein, "Reg1 $\alpha$ " refers to a polypeptide molecule having the sequence of either of SEQ ID Nos 2 or 4. Reg1 $\alpha$  as used herein, also refers to a polypeptide which is encoded by  
10 either of the sequences of SEQ ID Nos. 1 or 3. The sequences of SEQ ID Nos 2 and 4 each represent a functional Reg1 $\alpha$  protein, but differ from each other by four amino acids in the leader sequence which is cleaved off during protein synthesis.

          As used herein, "TIMP1" refers to a polypeptide molecule having the sequence of SEQ ID NO: 100. TIMP1 as used herein, also refers to a nucleotide which is encoded by the sequence  
15 of SEQ ID NO: 33, or a functional homolog thereof.

          As used herein, a "clinical sample" refers to a tissue, cellular, or fluid sample obtained from an individual. A "clinical sample", as used herein, can refer to a cells, circulating cells (e.g., circulating cells in blood), cells obtained from specific anatomical locations, or specific cell types (e.g., colon cell, gastrointestinal cell, cancerous cell, etc.), a tissue sample, or physiological  
20 fluids such as lymph, bile, serum, plasma, urine, synovial fluid, blood, CSF, mucus membrane secretions, or other physiological samples such as stool. Preferably, the clinical sample is serum or plasma. A colorectal cancer associated marker of the invention, such as TIMP1, may be detected in a suitable "clinical sample" where the suitability of a particular type of clinical sample for the detection of a specific colorectal cancer associated marker may be readily  
25 determined by one of skill in the art.

          As used herein, "detecting" refers to the identification of the presence or absence of a molecule in a sample. Where the molecule to be detected is a polypeptide, the step of detecting can be performed by binding the polypeptide with an antibody that is detectably labeled. A detectable label is a molecule which is capable of generating, either independently, or in  
30 response to a stimulus, an observable signal. A detectable label can be, but is not limited to a fluorescent label, a chromogenic label, a luminescent label, or a radioactive label. Methods for

“detecting” a label include quantitative and qualitative methods adapted for standard or confocal microscopy, FACS analysis, and those adapted for high throughput methods involving multiwell plates, arrays or microarrays. One of skill in the art can select appropriate filter sets and excitation energy sources for the detection of fluorescent emission from a given fluorescent polypeptide or dye. “Detecting” as used herein can also include the use of multiple antibodies to a polypeptide to be detected, wherein the multiple antibodies bind to different epitopes on the polypeptide to be detected. Antibodies used in this manner can employ two or more detectable labels, and can include, for example a FRET pair. A polypeptide molecule, such as Reg1 $\alpha$ , is “detected” according to the present invention when the level of detectable signal is at all greater than the background level of the detectable label, or where the level of measured nucleic acid is at all greater than the level measured in a control sample.

As used herein, “detecting” as it refers to detecting the presence of a target nucleic acid molecule (e.g., a nucleic acid molecule encoding Reg1 $\alpha$ , or other colorectal cancer-specific sequence) refers to a process wherein the signal generated by a directly or indirectly labeled probe nucleic acid molecule (capable of hybridizing to a target, e.g., a sequence encoding Reg1 $\alpha$ , in a serum sample) is measured or observed. Thus, detection of the probe nucleic acid is directly indicative of the presence, and thus the detection, of a target nucleic acid, such as a sequence encoding Reg1 $\alpha$ . For example, if the detectable label is a fluorescent label, the target nucleic acid (e.g., the nucleic acid molecule encoding Reg1 $\alpha$ ) is “detected” by observing or measuring the light emitted by the fluorescent label on the probe nucleic acid when it is excited by the appropriate wavelength, or if the detectable label is a fluorescence/quencher pair, the target nucleic acid is “detected” by observing or measuring the light emitted upon association or dissociation of the fluorescence/quencher pair present on the probe nucleic acid, wherein detection of the probe nucleic acid indicates detection of the target nucleic acid. If the detectable label is a radioactive label, the target nucleic acid, following hybridization with a radioactively labeled probe is “detected” by, for example, autoradiography. Methods and techniques for “detecting” fluorescent, radioactive, and other chemical labels may be found in Ausubel et al. (1995, Short Protocols in Molecular Biology, 3<sup>rd</sup> Ed. John Wiley and Sons, Inc.). Alternatively, a nucleic acid may be “indirectly detected” wherein a moiety is attached to a probe nucleic acid which will hybridize with the target, such as an enzyme activity, allowing detection in the presence of an appropriate substrate, or a specific antigen or other marker allowing detection by addition of an antibody or other specific indicator. Alternatively, a target nucleic acid molecule can be detected by amplifying a nucleic acid sample prepared from a patient clinical sample,

using oligonucleotide primers which are specifically designed to hybridize with a portion of the target nucleic acid sequence. Quantative amplification methods, such as, but not limited to TaqMan, may also be used to “detect” a target nucleic acid according to the invention. A nucleic acid molecule is “detected” as used herein where the level of nucleic acid measured (such as by  
5 quantitative PCR), or the level of detectable signal provided by the detectable label is at all above the background level.

As used herein, “detecting” refers further to the early detection of colorectal cancer in a patient, wherein “early” detection refers to the detection of colorectal cancer at Dukes stage A or preferably, prior to a time when the colorectal cancer is morphologically able to be classified in a  
10 particular Dukes stage. “Detecting” as used herein further refers to the detection of colorectal cancer recurrence in an individual, using the same detection criteria as indicated above. “Detecting” as used herein still further refers to the measuring of a change in the degree of colorectal cancer before and/or after treatment with a therapeutic agent. In this case, a change in the degree of colorectal cancer in response to a therapeutic agent refers to an increase or decrease  
15 in the expression of Reg1 $\alpha$  (and optionally, one or more additional colorectal cancer associated markers), or alternatively, in the amount of Reg1 $\alpha$  polypeptide (and optionally, one or more additional colorectal cancer associated markers) present in a clinical sample by at least 10% in response to the presence of a therapeutic agent relative to the expression level in the absence of the therapeutic agent.

20 As used herein, “individual” refers to a mammal, preferably a human.

As used herein, a “ligand” refers to a molecule which is capable of binding a polypeptide. A “polypeptide ligand” useful in the present invention includes, but is not limited to an antibody, a monoclonal antibody, a polyclonal antibody, an antibody fragment (e.g., Fv, scFV, or Fab), a small molecule, or a nucleic acid aptamer. A “ligand” as used herein can also refer to a “nucleic  
25 acid ligand”, such as an oligonucleotide, polynucleotide, DNA, RNA, mRNA, or cDNA, which is capable of binding to a complementary nucleic acid molecule, or polypeptide molecule.

The term “antibody” as used herein is intended to include whole antibodies, e.g., of any isotype (IgG, IgA, IgM, IgE, etc), and includes fragments thereof, and single-chain antibodies, which also are specifically reactive with a vertebrate, e.g., mammalian, protein. Antibodies can  
30 be fragmented using conventional techniques and the fragments screened for utility in the same manner as described above for whole antibodies. Thus, the term includes segments of

proteolytically-cleaved or recombinantly-prepared portions of an antibody molecule that are capable of selectively reacting with a certain protein. Nonlimiting examples of such proteolytic and/or recombinant fragments include Fab, F(ab')<sub>2</sub>, Fab', Fv, and single chain antibodies (scFv) containing a V[L] and/or V[H] domain joined by a peptide linker. The scFv's may be covalently  
5 or non-covalently linked to form antibodies having two or more binding sites. The subject invention includes polyclonal, monoclonal, or other purified preparations of antibodies and recombinant antibodies.

As used herein, a "colorectal cancer associated marker" refers to a polypeptide or nucleic acid sequence which exhibits over- or underexpression of at least 10% in colorectal  
10 cancer cells, tissue, or serum obtained from an individual having colorectal cancer, relative to the level of expression in cells, tissue, or serum obtained from an individual that does not have colorectal cancer. Non-limiting examples of colorectal cancer associated markers useful in the present invention include the nucleic acid molecules of SEQ ID Nos 1, 3, 5-71, and/or the polypeptide molecules of SEQ ID Nos 2, 4, 72-138. In one embodiment, the polypeptide  
15 sequences of SEQ ID Nos 2, 4, 72-138 are encoded by the nucleic acid sequences of 1, 3, 5-71, respectively. A "colorectal cancer specific marker" useful in the invention may be a polypeptide or nucleic acid sequence which exhibits over- or underexpression in colorectal cancer as described above, but which may also be over or underexpressed in other, non-colorectal types of cancer. Alternatively, a "colorectal cancer associated marker", as used herein, may refer to a  
20 carbohydrate epitope present on a polypeptide or nucleic acid molecule and/or an antibody molecule which recognizes and is capable of binding to such an epitope, wherein the carbohydrate epitope is known to be associated with the presence of colorectal cancer in an individual. Such carbohydrate epitopes may be present on more than one unrelated protein or polypeptide. In one embodiment, such a carbohydrate epitope is CA 19-9, also known as sialyl-  
25 Lewis<sup>a</sup>, is a tumor marker defined by a monoclonal antibody as a carbohydrate epitope, related to the blood group antigens, composed of a branching, 5-sugar structure covalently bound to a variety of glycoproteins or glycolipids. The proteins primarily belong to the mucin family and the lipids are usually membrane associated. The CA 19-9 epitope is typically the terminal moiety of a complex, O-linked carbohydrate structure on either macromolecule. Other tumor  
30 markers also defined as various carbohydrate epitopes useful in the present invention as a "colorectal cancer associated marker" include CA 72-4, TF, sTn, Tn, CA 50, CA 549, CA 242, LASA, and the Du-PAN's 1 -5.

The term “interact” as used herein is meant to include detectable interactions (e.g., biochemical interactions) between molecules, such as interaction between protein-protein, protein-nucleic acid, nucleic acid-nucleic acid, and protein-small molecule or nucleic acid-small molecule in nature.

5 As used herein, the term “nucleic acid” refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). The term should also be understood to include, as equivalents, analogs of either RNA or DNA made from nucleotide analogs, and, as applicable to the embodiment being described, single (sense or antisense) and double-stranded polynucleotides. ESTs, chromosomes, cDNAs, mRNAs, and  
10 rRNAs are representative examples of molecules that may be referred to as nucleic acids.

The terms “protein”, “polypeptide”, and “peptide” are used interchangeably herein when referring to a gene product. As used herein, “polypeptide” refers to any kind of polypeptide such as peptides, human proteins, fragments of human proteins, proteins or fragments of proteins from non-human sources, engineered versions proteins or fragments of proteins, enzymes, antigens,  
15 drugs, molecules involved in cell signaling, such as receptor molecules, antibodies, including polypeptides of the immunoglobulin superfamily, such as antibody polypeptides or T-cell receptor polypeptides.

As used herein, the term “level of expression” refers to the measurable expression level of a given nucleic acid. The level of expression of a nucleic acid is determined by methods well  
20 known in the art. The “level of expression” may measured by hybridization analysis using labeled target nucleic acids according to methods well known in the art (see, for example, Ausubel et al., Short Protocols in Molecular Biology, 3<sup>rd</sup> Ed. 1995, John Wiley and Sons, Inc.). The label on the target nucleic acid is a luminescent label, an enzymatic label, a radioactive label, a chemical label or a physical label. Preferably, the target nucleic acids are labeled with a  
25 fluorescent molecule. Preferred fluorescent labels include fluorescein, amino coumarin acetic acid, tetramethylrhodamine isothiocyanate (TRITC), Texas Red, Cy3 and Cy5. Alternatively, the “level of expression” can be measured by quantitative amplification protocols, such as TaqMan, known to those of skill in the art.

The term “vector” refers to a nucleic acid molecule capable of transporting another  
30 nucleic acid to which it has been linked. One type of preferred vector is an episome, i.e., a nucleic acid capable of extra-chromosomal replication. Preferred vectors are those capable of

autonomous replication and/or expression of nucleic acids to which they are linked. Vectors capable of directing the expression of genes to which they are operatively linked are referred to herein as "expression vectors". In general, expression vectors of utility in recombinant DNA techniques are often in the form of "plasmids" which refer generally to circular double stranded DNA loops which, in their vector form are not bound to the chromosome. In the present specification, "plasmid" and "vector" are used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors which serve equivalent functions and which become known in the art subsequently hereto.

10 Reg1 $\alpha$  and TIMP1 nucleic acid

As described above, the present invention relates to the detection of Reg1 $\alpha$  or TIMP1 polypeptide in a clinical sample from an individual, preferably a serum or plasma sample, thus permitting the detection of colorectal cancer. The present invention, however, equally relates to the identification of the nucleic acid sequence which encodes Reg1 $\alpha$  or TIMP1 as a marker for colorectal cancer.

Nucleic acid and amino acid sequences of Reg1 $\alpha$  are shown in SEQ ID Nos 1 or 3, and 2 or 4, respectively. Nucleic acid and amino acid sequences of TIMP1 are shown in SEQ ID NO: 33 and 100 respectively. While the invention relates to the direct detection of either of the sequences of Reg1 $\alpha$  or TIMP1 in a method for detecting colorectal cancer, the invention further relates to the detection of sequences complementary thereto, or a sequence which specifically hybridizes to a sequence of SEQ ID Nos. 1, 3, or 33. The present invention also relates to the detection of colorectal cancer by detecting the presence, in a clinical sample, of a nucleic acid molecule which encodes the sequence of SEQ ID Nos. 2, 4, or 100, or a fragment thereof.

Another aspect of the invention provides the detection of colorectal cancer by the detection of a nucleic acid which hybridizes under low, medium, or high stringency conditions to a nucleic acid sequence represented by one or more of SEQ ID Nos. 1, 3, or 33, or a sequence complementary thereto. Appropriate stringency conditions which promote DNA hybridization, for example, 6.0 x sodium chloride/sodium citrate (SSC) at about 45 °C, followed by a wash of 2.0 x SSC at 50°C, are known to those skilled in the art or can be found in Current Protocols in Molecular Biology, John Wiley & Sons, N.Y. (1989), 6.3.1-12.3.6. For example, the salt concentration in the wash step can be selected from a low stringency of about 2.0 x SSC at 50°C to a high stringency of about 0.2 x SSC at 50°C. In addition, the temperature in the wash step

can be increased from low stringency conditions at room temperature, about 22 °C, to high stringency conditions at about 65 °C. Both temperature and salt may be varied, or temperature or salt concentration may be held constant while the other variable is changed. In a preferred embodiment, a nucleic acid encoding Reg1α or TIMP1 will bind to SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, or a fragment thereof, under moderately stringent conditions, for example at about 2.0 x SSC and about 40°C. In a particularly preferred embodiment, a Reg1α or TIMP1 nucleic acid sequence present in a patient clinical sample will bind of SEQ ID Nos. 1, 3, or 33, respectively, or a sequence complementary thereto, or fragment thereof, under high stringency conditions.

10 In one embodiment, the invention provides nucleic acids which hybridize under low stringency conditions of 6 x SSC at room temperature followed by a wash at 2 x SSC at room temperature.

In another embodiment, the invention provides nucleic acids which hybridize under high stringency conditions of 2 x SSC at about 65 °C followed by a wash at 0.2 x SSC at about 65 °C.

15 Detection of Reg1α nucleic acids having a sequence that differs from the nucleotide sequences shown in SEQ ID Nos. 1 or 3, or a sequence complementary thereto, due to degeneracy in the genetic code, are also within the scope of the invention. Such nucleic acids encode functionally equivalent peptides (i.e., a peptide having equivalent or similar biological activity) but differ in sequence from the sequence shown in the sequence listing due to  
20 degeneracy in the genetic code. For example, a number of amino acids are designated by more than one triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC each encode histidine) may result in "silent" mutations which do not affect the amino acid sequence of a polypeptide. However, it is expected that DNA sequence polymorphisms that do lead to changes in the amino acid sequences of the subject polypeptides will exist among  
25 mammals. One skilled in the art will appreciate that these variations in one or more nucleotides (e.g., up to about 3-5% of the nucleotides) of the nucleic acids encoding polypeptides having an activity of a polypeptide may exist among individuals of a given species due to natural allelic variation.

The invention also includes within its scope a polynucleotide which hybridizes under  
30 stringent conditions (at least about 4 x SSC at 65 °C, or at least about 4 x SSC at 42 °C; see, for example, U.S. Patent No. 5,707,829, incorporated herein by reference) with at least 15



contiguous nucleotides of SEQ ID Nos. 1 or 3. By this is intended that when at least 15 contiguous nucleotides of SEQ ID Nos. 1 or 3 is used as a probe, the probe will preferentially hybridize with a gene or mRNA (of the biological material) comprising the complementary sequence, allowing the identification and retrieval of the nucleic acids (i.e., Reg1 $\alpha$ ) of the biological material that uniquely hybridize to the selected probe. Probes of more than 15 nucleotides can be used, but 15 nucleotides represents enough sequence for unique identification.

Constructs of polynucleotides having the sequence of SEQ ID Nos. 1 or 3, a portion thereof, or a sequence complementary thereto, and useful, for example for generating a probe, can be produced synthetically, or obtained from natural sources (e.g., human cells) using methods well known to those of skill in the art (see, for example, Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989).

#### *Calculation of Sequence Homology*

In one embodiment, the present invention relates to the detection of colorectal cancer in an individual by detecting the presence of Reg1 $\alpha$  or TIMP1 or a sequence homologous thereto, by using probes and/or primers which are complementary to portions of the Reg1 $\alpha$  or TIMP1 sequence, or are sufficiently homologous to portions of the Reg1 $\alpha$  or TIMP1 sequence to permit hybridization of the probes and/or primers to Reg1 $\alpha$  or TIMP1 under high stringency conditions. Sequences of the invention are at least 50% homologous to Reg1 $\alpha$  or TIMP1, and are preferably 60%, 70%, 80%, 90% homologous up to complete sequence identity with Reg1 $\alpha$  or TIMP1 (or optionally to a sequence encoding one or more additional colorectal cancer associated markers).

Sequence identity with respect to any of the sequences presented herein can be determined by a simple "eyeball" comparison (i.e. a strict comparison) of any one or more of the sequences with another sequence to see if that other sequence has, for example, at least 80% sequence identity to the sequence(s).

Relative sequence identity can also be determined by commercially available computer programs that can calculate % identity between two or more sequences using any suitable algorithm for determining identity, using for example default parameters. A typical example of such a computer program is CLUSTAL. Other computer program methods to determine identity and similarity between two sequences include but are not limited to the GCG program package

(Devereux *et al* 1984 Nucleic Acids Research 12: 387) and FASTA (Atschul *et al* 1990 J Molec Biol 403-410).

% homology may be calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each amino acid in one sequence is directly compared with the  
5 corresponding amino acid in the other sequence, one residue at a time. This is called an “ungapped” alignment. Typically, such ungapped alignments are performed only over a relatively short number of residues.

Although this is a very simple and consistent method, it fails to take into consideration that, for example, in an otherwise identical pair of sequences, one insertion or deletion will cause  
10 the following amino acid residues to be put out of alignment, thus potentially resulting in a large reduction in % homology when a global alignment is performed. Consequently, most sequence comparison methods are designed to produce optimal alignments that take into consideration possible insertions and deletions without penalising unduly the overall homology score. This is achieved by inserting “gaps” in the sequence alignment to try to maximise local homology.

15 However, these more complex methods assign “gap penalties” to each gap that occurs in the alignment so that, for the same number of identical amino acids, a sequence alignment with as few gaps as possible - reflecting higher relatedness between the two compared sequences - will achieve a higher score than one with many gaps. “Affine gap costs” are typically used that charge a relatively high cost for the existence of a gap and a smaller penalty for each subsequent residue  
20 in the gap. This is the most commonly used gap scoring system. High gap penalties will of course produce optimized alignments with fewer gaps. Most alignment programs allow the gap penalties to be modified. However, it is preferred to use the default values when using such software for sequence comparisons. For example, when using the GCG Wisconsin Bestfit package the default gap penalty for amino acid sequences is -12 for a gap and -4 for each  
25 extension.

Calculation of maximum % homology therefore firstly requires the production of an optimal alignment, taking into consideration gap penalties. A suitable computer program for carrying out such an alignment is the GCG Wisconsin Bestfit package (University of Wisconsin, U.S.A.; Devereux *et al.*, 1984, Nucleic Acids Research 12:387). Examples of other software that  
30 can perform sequence comparisons include, but are not limited to, the BLAST package (Ausubel *et al.*, 1995, Short Protocols in Molecular Biology, 3rd Edition, John Wiley & Sons), FASTA

(Atschul *et al.*, 1990, J. Mol. Biol., 403-410) and the GENWORKS suite of comparison tools. Both BLAST and FASTA are available for offline and online searching (Ausubel *et al.*, 1999 *supra*, pages 7-58 to 7-60).

Although the final % homology can be measured in terms of identity, the alignment  
5 process itself is typically not based on an all-or-nothing pair comparison. Instead, a scaled  
similarity score matrix is generally used that assigns scores to each pairwise comparison based on  
chemical similarity or evolutionary distance. An example of such a matrix commonly used is the  
BLOSUM62 matrix - the default matrix for the BLAST suite of programs. GCG Wisconsin  
programs generally use either the public default values or a custom symbol comparison table if  
10 supplied. It is preferred to use the public default values for the GCG package, or in the case of  
other software, the default matrix, such as BLOSUM62.

Advantageously, the BLAST algorithm is employed, with parameters set to default values.  
The BLAST algorithm is described in detail on the World Wide Web at  
ncbi.nih.gov/BLAST/blast\_help.html, which is incorporated herein by reference. The search  
15 parameters are defined as follows, and can be advantageously set to the defined default  
parameters.

Advantageously, "substantial identity" when assessed by BLAST equates to sequences  
which match with an EXPECT value of at least about 7, preferably at least about 9 and most  
preferably 10 or more. The default threshold for EXPECT in BLAST searching is usually 10.

20 BLAST (Basic Local Alignment Search Tool) is the heuristic search algorithm employed  
by the programs blastp, blastn, blastx, tblastn, and tblastx; these programs ascribe significance to  
their findings using the statistical methods of Karlin and Altschul (Karlin and Altschul 1990, *Proc.*  
*Natl. Acad. Sci. USA* 87:2264-68; Karlin and Altschul, 1993, *Proc. Natl. Acad. Sci. USA* 90:5873-  
7; see [http://www.ncbi.nih.gov/BLAST/blast\\_help.html](http://www.ncbi.nih.gov/BLAST/blast_help.html)) with a few enhancements. The BLAST  
25 programs are tailored for sequence similarity searching, for example to identify homologues to a  
query sequence. For a discussion of basic issues in similarity searching of sequence databases, see  
Altschul *et al* (1994) *Nature Genetics* 6:119-129.

The five BLAST programs available on the World Wide Web at ncbi.nlm.nih.gov perform  
the following tasks: **blastp** - compares an amino acid query sequence against a protein sequence  
30 database; **blastn** - compares a nucleotide query sequence against a nucleotide sequence database;  
**blastx** - compares the six-frame conceptual translation products of a nucleotide query sequence

(both strands) against a protein sequence database; **tblastn** - compares a protein query sequence against a nucleotide sequence database dynamically translated in all six reading frames (both strands); **tblastx** - compares the six-frame translations of a nucleotide query sequence against the six-frame translations of a nucleotide sequence database.

5       BLAST uses the following search parameters:

HISTOGRAM - Display a histogram of scores for each search; default is yes. (See parameter H in the BLAST Manual).

DESCRIPTIONS - Restricts the number of short descriptions of matching sequences reported to the number specified; default limit is 100 descriptions. (See parameter V in the manual  
10   page).

EXPECT - The statistical significance threshold for reporting matches against database sequences; the default value is 10, such that 10 matches are expected to be found merely by chance, according to the stochastic model of Karlin and Altschul (1990). If the statistical significance ascribed to a match is greater than the EXPECT threshold, the match will not be  
15   reported. Lower EXPECT thresholds are more stringent, leading to fewer chance matches being reported. Fractional values are acceptable. (See parameter E in the BLAST Manual).

CUTOFF - Cutoff score for reporting high-scoring segment pairs. The default value is calculated from the EXPECT value (see above). HSPs are reported for a database sequence only if the statistical significance ascribed to them is at least as high as would be ascribed to a lone HSP  
20   having a score equal to the CUTOFF value. Higher CUTOFF values are more stringent, leading to fewer chance matches being reported. (See parameter S in the BLAST Manual). Typically, significance thresholds can be more intuitively managed using EXPECT.

ALIGNMENTS - Restricts database sequences to the number specified for which high-scoring segment pairs (HSPs) are reported; the default limit is 50. If more database sequences  
25   than this happen to satisfy the statistical significance threshold for reporting (see EXPECT and CUTOFF below), only the matches ascribed the greatest statistical significance are reported. (See parameter B in the BLAST Manual).

MATRIX - Specify an alternate scoring matrix for BLASTP, BLASTX, TBLASTN and TBLASTX. The default matrix is BLOSUM62 (Henikoff & Henikoff, 1992). The valid  
30   alternative choices include: PAM40, PAM120, PAM250 and IDENTITY. No alternate scoring

matrices are available for BLASTN; specifying the MATRIX directive in BLASTN requests returns an error response.

STRAND - Restrict a TBLASTN search to just the top or bottom strand of the database sequences; or restrict a BLASTN, BLASTX or TBLASTX search to just reading frames on the top  
5 or bottom strand of the query sequence.

FILTER - Mask off segments of the query sequence that have low compositional complexity, as determined by the SEG program of Wootton & Federhen (1993) Computers and Chemistry 17:149-163, or segments consisting of short-periodicity internal repeats, as determined by the XNU program of Claverie & States (1993) Computers and Chemistry 17:191-201, or, for  
10 BLASTN, by the DUST program of Tatusov and Lipman (see <http://www.ncbi.nlm.nih.gov>). Filtering can eliminate statistically significant but biologically uninteresting reports from the blast output (e.g., hits against common acidic-, basic- or proline-rich regions), leaving the more biologically interesting regions of the query sequence available for specific matching against database sequences.

15 Low complexity sequence found by a filter program is substituted using the letter "N" in nucleotide sequence (e.g., "NNNNNNNNNNNNNN") and the letter "X" in protein sequences (e.g., "XXXXXXXXXX").

Filtering is only applied to the query sequence (or its translation products), not to database sequences. Default filtering is DUST for BLASTN, SEG for other programs.

20 It is not unusual for nothing at all to be masked by SEG, XNU, or both, when applied to sequences in SWISS-PROT, so filtering should not be expected to always yield an effect. Furthermore, in some cases, sequences are masked in their entirety, indicating that the statistical significance of any matches reported against the unfiltered query sequence should be suspect.

NCBI-gi - Causes NCBI gi identifiers to be shown in the output, in addition to the  
25 accession and/or locus name.

Most preferably, sequence comparisons are conducted using the simple BLAST search algorithm provided on the World Wide Web at [ncbi.nlm.nih.gov/BLAST](http://ncbi.nlm.nih.gov/BLAST). In some embodiments of the present invention, no gap penalties are used when determining sequence identity.

## Probes and Primers

The nucleotide sequence of Reg1 $\alpha$  or TIMP1 is useful in the present invention for the generation of probes and primers designed for identifying the Reg1 $\alpha$  or TIMP1 nucleic acid sequence in a patient sample such as serum, colon cells or tissue. Nucleotide sequences useful as probes/primers may include all or a portion of SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, or sequences which hybridize under stringent conditions to all or a portion of SEQ ID No. 1, 3 or 33. For instance, the present invention also provides a probe/primer comprising a substantially purified oligonucleotide, which oligonucleotide comprising a nucleotide sequence that hybridizes under stringent conditions to at least approximately 8, preferably about 12, preferably about 15, preferably about 25, more preferably about 40 consecutive nucleotides up to the full length of the sense or anti-sense sequence of SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, or a naturally occurring mutant thereof. For instance, primers based on the nucleic acid represented in SEQ ID No. 1, 3 or 33, or a sequence complementary thereto, can be used in a reaction to amplify a template nucleic acid (e.g., Reg1 $\alpha$ ) contained within an mRNA sample derived from a patient clinical sample.

Not only are probes based on the nucleic acid sequence encoding Reg1 $\alpha$  or TIMP1 useful for detecting Reg1 $\alpha$  or TIMP1, but they can also provide a method for detecting mutations in wild-type Reg1 $\alpha$  or TIMP1 in a patient. Nucleic acid probes which are complementary to a wild-type Reg1 $\alpha$  or TIMP1 and can form mismatches with mutant genes are provided, allowing for detection by enzymatic or chemical cleavage or by shifts in electrophoretic mobility. Likewise, probes based on the subject sequences can be used to detect transcripts or genomic sequences encoding the same or homologous proteins, for use, for example, in prognostic or diagnostic assays. In preferred embodiments, the nucleic acid probe further comprises a label group attached thereto and able to be detected, e.g., the label group is selected from a radioisotope, a fluorescent compound, a chemiluminescent compound, a chromagenic compound, an enzyme, and enzyme co-factor.

Full-length cDNA molecules comprising the disclosed nucleic acids, useful for the generation of probes, primers, or for transcription to produce the Reg1 $\alpha$  or TIMP1 protein itself, or antibodies thereto may be obtained as follows. The nucleic acid sequence of Reg1 $\alpha$  or TIMP1 or a portion thereof comprising at least approximately 8, preferably about 12, preferably about 15, preferably about 25, more preferably about 40 nucleotides up to the full length of the sequence of SEQ ID Nos. 1, 3 or 33, or a sequence complementary thereto, may be used as a

hybridization probe to detect hybridizing members of a cDNA library using probe design methods, cloning methods, and clone selection techniques as described in U.S. Patent No. 5,654,173, "Secreted Proteins and Polynucleotides Encoding Them," incorporated herein by reference. Libraries of cDNA may be made from selected tissues, such as normal or tumor tissue, or from tissues of a mammal treated with, for example, a pharmaceutical agent. Preferably, the tissue is the same as that used to generate the nucleic acids, as both the nucleic acid and the cDNA represent expressed genes. Alternatively, many cDNA libraries are available commercially. (Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989). The choice of cell type for library construction may be made after the identity of the protein encoded by the nucleic acid-related gene is known. This will indicate which tissue and cell types are likely to express the related gene, thereby containing the mRNA for generating the cDNA.

Members of the library that are larger than the nucleic acid, and preferably that contain the whole sequence of the native message, may be obtained. To confirm that the entire cDNA has been obtained, RNA protection experiments may be performed as follows. Hybridization of a full-length cDNA to an mRNA may protect the RNA from RNase degradation. If the cDNA is not full length, then the portions of the mRNA that are not hybridized may be subject to RNase degradation. This may be assayed, as is known in the art, by changes in electrophoretic mobility on polyacrylamide gels, or by detection of released monoribonucleotides. Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed. (Cold Spring Harbor Press, Cold Spring Harbor, NY 1989). In order to obtain additional sequences 5' to the end of a partial cDNA, 5' RACE (PCR Protocols: A Guide to Methods and Applications (Academic Press, Inc. 1990)) may be performed.

Genomic DNA (e.g., Reg1a genomic DNA) may be isolated using nucleic acids in a manner similar to the isolation of full-length cDNAs. Briefly, the nucleic acids, or portions thereof, may be used as probes to libraries of genomic DNA. Preferably, the library is obtained from the cell type that was used to generate the nucleic acids. Most preferably, the genomic DNA is obtained from the biological material described herein in the Example. Such libraries may be in vectors suitable for carrying large segments of a genome, such as P1 or YAC, as described in detail in Sambrook et al., pages 9.4-9.30. In addition, genomic sequences can be isolated from human BAC libraries, which are commercially available from Research Genetics, Inc., Huntsville, Alabama, USA, for example. In order to obtain additional 5' or 3' sequences,

chromosome walking may be performed, as described in Sambrook et al., such that adjacent and overlapping fragments of genomic DNA are isolated. These may be mapped and pieced together, as is known in the art, using restriction digestion enzymes and DNA ligase.

Using the nucleic acids of the invention, corresponding full length genes can be isolated  
5 using both classical and PCR methods to construct and probe cDNA libraries. Using either method, Northern blots, preferably, may be performed on a number of cell types to determine which cell lines express the gene of interest at the highest rate.

Classical methods of constructing cDNA libraries in Sambrook et al., supra. With these methods, cDNA can be produced from mRNA and inserted into viral or expression vectors.  
10 Typically, libraries of mRNA comprising poly(A) tails can be produced with poly(T) primers. Similarly, cDNA libraries can be produced using the instant Reg1 $\alpha$  sequence or portions thereof as primers.

PCR methods may be used to amplify the members of a cDNA library that comprise the desired insert. In this case, the desired insert may contain sequence from the full length cDNA  
15 that corresponds to the sequence encoding Reg1 $\alpha$ . Such PCR methods include gene trapping and RACE methods.

Gene trapping may entail inserting a member of a cDNA library into a vector. The vector then may be denatured to produce single stranded molecules. Next, a substrate-bound probe, such a biotinylated oligo, may be used to trap cDNA inserts of interest. Biotinylated probes can  
20 be linked to an avidin-bound solid substrate. PCR methods can be used to amplify the trapped cDNA. To trap sequences corresponding to the full length genes, the labeled probe sequence may be based on the nucleic acid of SEQ ID Nos. 1 or 3, or a sequence complementary thereto. Random primers or primers specific to the library vector can be used to amplify the trapped cDNA. Such gene trapping techniques are described in Gruber et al., PCT WO 95/04745 and  
25 Gruber et al., U.S. Pat. No. 5,500,356. Kits are commercially available to perform gene trapping experiments from, for example, Life Technologies, Gaithersburg, Maryland, USA.

"Rapid amplification of cDNA ends," or RACE, is a PCR method of amplifying cDNAs from a number of different RNAs. The cDNAs may be ligated to an oligonucleotide linker and amplified by PCR using two primers. One primer may be based on sequence from the instant  
30 nucleic acids, for which full length sequence is desired, and a second primer may comprise a



sequence that hybridizes to the oligonucleotide linker to amplify the cDNA. A description of this method is reported in PCT Pub. No. WO 97/19110.

In preferred embodiments of RACE, a common primer may be designed to anneal to an arbitrary adaptor sequence ligated to cDNA ends (Apte and Siebert, Biotechniques 15:890-893, 1993; Edwards et al., Nuc. Acids Res. 19:5227-5232, 1991). When a single gene-specific RACE primer is paired with the common primer, preferential amplification of sequences between the single gene specific primer and the common primer occurs. Commercial cDNA pools modified for use in RACE are available.

Once the full-length cDNA or gene is obtained, DNA encoding variants can be prepared by site-directed mutagenesis, described in detail in Sambrook 15.3-15.63. The choice of codon or nucleotide to be replaced can be based on the disclosure herein on optional changes in amino acids to achieve altered protein structure and/or function.

As an alternative method to obtaining DNA or RNA from a biological material, such as serum, nucleic acid comprising nucleotides having the sequence of one or more nucleic acids of the invention can be synthesized. Thus, the invention encompasses nucleic acid molecules ranging in length from about 8 nucleotides (corresponding to at least 12 contiguous nucleotides which hybridize under stringent conditions to or are at least 80% identical to the nucleic acid sequence of SEQ ID Nos. 1 or 3, or a sequence complementary thereto) up to a maximum length suitable for one or more biological manipulations, including replication and expression, of the nucleic acid molecule. The invention includes but is not limited to (a) nucleic acid having the size of the full Reg I $\alpha$  gene, or a sequence complementary thereto; (b) the nucleic acid of (a) also comprising at least one additional gene, operably linked to permit expression of a fusion protein; (c) an expression vector comprising (a) or (b); (d) a plasmid comprising (a) or (b); and (e) a recombinant viral particle comprising (a) or (b).

The sequence of a nucleic acid of the present invention is not limited and can be any sequence of A, T, G, and/or C (for DNA) and A, U, G, and/or C (for RNA) or modified bases thereof, including inosine and pseudouridine. The choice of sequence will depend on the desired function and can be dictated by coding regions desired, the intron-like regions desired, and the regulatory regions desired.

### *Probe preparation*

Prior to hybridization of a probe nucleic acid to a patient sample, the nucleic acid samples must be prepared to facilitate subsequent detection of hybridization. The nucleic acid samples obtained from an individual (including nucleic acid sequences encoding Reg1 $\alpha$ , and optionally, at least one other colorectal cancer associated marker) to be screened for colorectal cancer are capable of being bound by a nucleic acid probe of complementary sequence through one or more types of chemical bonds, usually through complementary base pairing, usually through hydrogen bond formation.

Probes useful in the invention for hybridizing to and thus identifying the presence of Reg1 $\alpha$  or TIMP1, and optionally, at least one additional colorectal cancer associated marker may be designed to hybridize to a polynucleotide molecule derived from an mRNA transcript coding for Reg1 $\alpha$ , or optionally, at least one additional colorectal cancer associated marker. As used herein, a "polynucleotide derived from an mRNA transcript" refers to a polynucleotide for which synthesis of the mRNA transcript or a subsequence thereof has ultimately served as a template. Thus, a cDNA reverse transcribed from an mRNA, an RNA transcribed from that cDNA, a DNA amplified from the cDNA, an RNA transcribed from the amplified DNA, etc., are all derived from the mRNA transcript and detection of such derived products is indicative of the presence and/or abundance of the original transcript in a sample. Thus, suitable target nucleic acid samples include, but are not limited to, mRNA transcripts of a gene or genes (i.e., Reg1 $\alpha$  or a colorectal cancer associated marker), cDNA reverse transcribed from the mRNA, cRNA transcribed from the cDNA, DNA amplified from a gene or genes, RNA transcribed from amplified DNA, and the like. The polynucleotide probes used herein are preferably designed to hybridize to Reg1 $\alpha$ , or optionally to a sequence encoding at least one other colorectal cancer associated marker.

Nucleic acid probes may be generated using techniques which are well known to those of skill in the art (see, e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual* (2nd ed.), Vols. 1-3, Cold Spring Harbor Laboratory, (1989), or *Current Protocols in Molecular Biology*, F. Ausubel et al., ed. Greene Publishing and Wiley-Interscience, New York (1987).

In order to measure the hybridization of a probe nucleic acid to a target sequence in a sample, the probe nucleic acid is preferably labeled with a detectable label. Any analytically detectable marker that is attached to or incorporated into a molecule may be used in the

invention. An analytically detectable marker refers to any molecule, moiety or atom which is analytically detected and quantified.

Detectable labels suitable for use in the present invention include any composition detectable by spectroscopic, photochemical, biochemical, immunochemical, electrical, optical or chemical means. Useful labels in the present invention include biotin for staining with labeled streptavidin conjugate, magnetic beads (e.g., Dynabeads™), fluorescent dyes (e.g., fluorescein, texas red, rhodamine, green fluorescent protein, and the like), radiolabels (e.g., <sup>3</sup>H, <sup>125</sup>I, <sup>35</sup>S, <sup>14</sup>C, or <sup>32</sup>P), enzymes (e.g., horse radish peroxidase, alkaline phosphatase and others commonly used in an ELISA), and colorimetric labels such as colloidal gold or colored glass or plastic (e.g., polystyrene, polypropylene, latex, etc.) beads. Patents teaching the use of such labels include U.S. Pat. Nos. 3,817,837; 3,850,752; 3,939,350; 3,996,345; 4,277,437; 4,275,149; and 4,366,241.

Means of detecting such labels are well known to those of skill in the art. Thus, for example, radiolabels may be detected using photographic film or scintillation counters, fluorescent markers may be detected using a photodetector to detect emitted light. Enzymatic labels are typically detected by providing the enzyme with a substrate and detecting the reaction product produced by the action of the enzyme on the substrate, and colorimetric labels are detected by simply visualizing the colored label.

The labels may be incorporated into a nucleic acid probe by any of a number of means well known to those of skill in the art. However, in a preferred embodiment, the label is simultaneously incorporated into the probe during an amplification step in the preparation of the probe polynucleotides. Thus, for example, polymerase chain reaction (PCR), or other amplification reaction, with labeled primers or labeled nucleotides will provide a labeled amplification product, and thus a labeled probe.

Alternatively, a label may be added directly to the probe. Means of attaching labels to polynucleotides are well known to those of skill in the art and include, for example nick translation or end-labeling (e.g. with a labeled RNA) and subsequent attachment (ligation) of a polynucleotide linker joining the sample polynucleotide to a label (e.g., a fluorophore).

In a preferred embodiment, the fluorescent modifications are by cyanine dyes e.g. Cy-3/Cy-5 dUTP, Cy-3/Cy-5 dCTP (Amersham Pharmacia) or alexa dyes (Khan, J., Simon, R.,

Bittner, M., Chen, Y., Leighton, S. B., Pohida, T., Smith, P. D., Jiang, Y., Gooden, G. C., Trent, J. M. & Meltzer, P. S. (1998) *Cancer Res.* 58, 50095013.).

In a preferred embodiment, a probe nucleic acid which is capable of hybridizing to Reg1 $\alpha$  and a probe nucleic acid which is capable of hybridizing to a nucleic acid sequence encoding at least one additional colorectal cancer associated marker, are co-hybridized to a test sample (e.g., a serum sample). In this embodiment, the two probe samples used for comparison are labeled with different fluorescent dyes which produce distinguishable detection signals, for example, probes hybridizable with Reg1 $\alpha$  are labeled with Cy5 and probes hybridizable with another colorectal cancer associated marker are labeled with Cy3. The differently labeled target samples are hybridized to the same microarray simultaneously.

In a preferred embodiment, a control probe may be co-hybridized to a sample along with a probe for Reg1 $\alpha$  and/or a probe for an additional colorectal cancer associated marker, wherein the control probe is capable of hybridizing to a nucleic acid sequence known to be found in the clinical sample, for example, where the clinical sample is a serum sample, a control sequence may be a sequence encoding serum albumin, or fibrinogen.

#### Vectors and Host Cells

The present invention further provides vectors and plasmids useful for directing the expression of Reg1 $\alpha$  or TIMP1 or other colorectal cancer associated markers, and further provides host cells which express the vectors and plasmids provided herein. Nucleic acid sequences useful for the expression from a vector or plasmid as described below include, but are not limited to any nucleic acid or gene sequence identified as being differentially regulated by the methods described above, and further include therapeutic nucleic acid molecules, such as antisense molecules. The host cell may be any prokaryotic or eukaryotic cell. Ligating the polynucleotide sequence into a gene construct, such as an expression vector, and transforming or transfecting into hosts, either eukaryotic (yeast, avian, insect or mammalian) or prokaryotic (bacterial cells), are standard procedures well known in the art.

#### *Vectors*

There is a wide array of vectors known and available in the art that are useful for the expression of differentially expressed nucleic acid molecules according to the invention. The selection of a particular vector clearly depends upon the intended use the polypeptide encoded by

the differentially expressed nucleic acid. For example, the selected vector must be capable of driving expression of the polypeptide in the desired cell type, whether that cell type be prokaryotic or eukaryotic. Many vectors comprise sequences allowing both prokaryotic vector replication and eukaryotic expression of operably linked gene sequences.

5            Vectors useful according to the invention may be autonomously replicating, that is, the vector, for example, a plasmid, exists extrachromosomally and its replication is not necessarily directly linked to the replication of the host cell's genome. Alternatively, the replication of the vector may be linked to the replication of the host's chromosomal DNA, for example, the vector may be integrated into the chromosome of the host cell as achieved by retroviral vectors.

10           Vectors useful according to the invention preferably comprise sequences operably linked to the sequence of interest (e.g., Reg1a) that permit the transcription and translation of the sequence. Sequences that permit the transcription of the linked sequence of interest include a promoter and optionally also include an enhancer element or elements permitting the strong expression of the linked sequences. The term "transcriptional regulatory sequences" refers to the  
15 combination of a promoter and any additional sequences conferring desired expression characteristics (e.g., high level expression, inducible expression, tissue- or cell-type-specific expression) on an operably linked nucleic acid sequence.

            The selected promoter may be any DNA sequence that exhibits transcriptional activity in the selected host cell, and may be derived from a gene normally expressed in the host cell or  
20 from a gene normally expressed in other cells or organisms. Examples of promoters include, but are not limited to the following: A) prokaryotic promoters - *E. coli* lac, tac, or trp promoters, lambda phage P<sub>R</sub> or P<sub>L</sub> promoters, bacteriophage T7, T3, Sp6 promoters, *B. subtilis* alkaline protease promoter, and the *B. stearothermophilus* maltogenic amylase promoter, etc.; B) eukaryotic promoters - yeast promoters, such as GAL1, GAL4 and other glycolytic gene  
25 promoters (see for example, Hitzeman et al., 1980, J. Biol. Chem. 255: 12073-12080; Alber & Kawaśaki, 1982, J. Mol. Appl. Gen. 1: 419-434), LEU2 promoter (Martinez-Garcia et al., 1989, Mol Gen Genet. 217: 464-470), alcohol dehydrogenase gene promoters (Young et al., 1982, in Genetic Engineering of Microorganisms for Chemicals, Hollaender et al., eds., Plenum Press, NY), or the TPI1 promoter (U.S. Pat. No. 4,599,311); insect promoters, such as the polyhedrin  
30 promoter (U.S. Pat. No. 4,745,051; Vasuvedan et al., 1992, FEBS Lett. 311: 7-11), the P10 promoter (Vlak et al., 1988, J. Gen. Virol. 69: 765-776), the *Autographa californica* polyhedrosis virus basic protein promoter (EP 397485), the baculovirus immediate-early gene promoter gene

1 promoter (U.S. Pat. Nos. 5,155,037 and 5,162,222), the baculovirus 39K delayed-early gene promoter (also U.S. Pat. Nos. 5,155,037 and 5,162,222) and the OpMNPV immediate early promoter 2; mammalian promoters - the SV40 promoter (Subramani et al., 1981, Mol. Cell. Biol. 1: 854-864), metallothionein promoter (MT-1; Palmiter et al., 1983, Science 222: 809-814),  
5 adenovirus 2 major late promoter (Yu et al., 1984, Nucl. Acids Res. 12: 9309-21), cytomegalovirus (CMV) or other viral promoter (Tong et al., 1998, Anticancer Res. 18: 719-725), or even the endogenous promoter of a gene of interest in a particular cell type.

A selected promoter may also be linked to sequences rendering it inducible or tissue-specific. For example, the addition of a tissue-specific enhancer element upstream of a selected  
10 promoter may render the promoter more active in a given tissue or cell type. Alternatively, or in addition, inducible expression may be achieved by linking the promoter to any of a number of sequence elements permitting induction by, for example, thermal changes (temperature sensitive), chemical treatment (for example, metal ion- or IPTG-inducible), or the addition of an antibiotic inducing agent (for example, tetracycline).

15 Regulatable expression is achieved using, for example, expression systems that are drug inducible (e.g., tetracycline, rapamycin or hormone-inducible). Drug-regulatable promoters that are particularly well suited for use in mammalian cells include the tetracycline regulatable promoters, and glucocorticoid steroid-, sex hormone steroid-, ecdysone-, lipopolysaccharide (LPS)- and isopropylthiogalactoside (IPTG)-regulatable promoters. A regulatable expression  
20 system for use in mammalian cells should ideally, but not necessarily, involve a transcriptional regulator that binds (or fails to bind) nonmammalian DNA motifs in response to a regulatory agent, and a regulatory sequence that is responsive only to this transcriptional regulator.

Tissue-specific promoters may also be used to advantage in differentially expressed sequence-encoding constructs of the invention. A wide variety of tissue-specific promoters is  
25 known. As used herein, the term "tissue-specific" means that a given promoter is transcriptionally active (i.e., directs the expression of linked sequences sufficient to permit detection of the polypeptide product of the promoter) in less than all cells or tissues of an organism. A tissue specific promoter is preferably active in only one cell type, but may, for example, be active in a particular class or lineage of cell types (e.g., hematopoietic cells). A  
30 tissue specific promoter useful according to the invention comprises those sequences necessary and sufficient for the expression of an operably linked nucleic acid sequence in a manner or pattern that is essentially the same as the manner or pattern of expression of the gene linked to

that promoter in nature. The following is a non-exclusive list of tissue specific promoters and literature references containing the necessary sequences to achieve expression characteristic of those promoters in their respective tissues; the entire content of each of these literature references is incorporated herein by reference. Examples of tissue specific promoters useful in the present invention are as follows:

Bowman et al., 1995 Proc. Natl. Acad. Sci. USA 92,12115-12119 describe a brain-specific transferrin promoter; the synapsin I promoter is neuron specific (Schoch et al., 1996 J. Biol. Chem. 271, 3317-3323); the nestin promoter is post-mitotic neuron specific (Uetsuki et al., 1996 J. Biol. Chem. 271, 918-924); the neurofilament light promoter is neuron specific (Charron et al., 1995 J. Biol. Chem. 270, 30604-30610); the acetylcholine receptor promoter is neuron specific (Wood et al., 1995 J. Biol. Chem. 270, 30933-30940); and the potassium channel promoter is high-frequency firing neuron specific (Gan et al., 1996 J. Biol. Chem. 271, 5859-5865). Any tissue specific transcriptional regulatory sequence known in the art may be used to advantage with a vector encoding a differentially expressed nucleic acid sequence obtained from an animal subjected to pain.

In addition to promoter/enhancer elements, vectors useful according to the invention may further comprise a suitable terminator. Such terminators include, for example, the human growth hormone terminator (Palmiter et al., 1983, supra), or, for yeast or fungal hosts, the TPI1 (Alber & Kawasaki, 1982, supra) or ADH3 terminator (McKnight et al., 1985, EMBO J. 4: 2093-2099).

Vectors useful according to the invention may also comprise polyadenylation sequences (e.g., the SV40 or Ad5E1b poly(A) sequence), and translational enhancer sequences (e.g., those from Adenovirus VA RNAs). Further, a vector useful according to the invention may encode a signal sequence directing the recombinant polypeptide to a particular cellular compartment or, alternatively, may encode a signal directing secretion of the recombinant polypeptide.

a. Plasmid vectors.

Any plasmid vector that allows expression of a coding sequence of interest (e.g., the coding sequence of Reg1 $\alpha$ ) in a selected host cell type is acceptable for use according to the invention. A plasmid vector useful in the invention may have any or all of the above-noted characteristics of vectors useful according to the invention. Plasmid vectors useful according to the invention include, but are not limited to the following examples: Bacterial - pQE70, pQE60, pQE-9 (Qiagen) pBs, phagescript, psiX174, pBluescript SK, pBsKS, pNH8a, pNH16a, pNH18a,

pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, and pRIT5 (Pharmacia); Eukaryotic - pWLneo, pSV2cat, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, and pSVL (Pharmacia). However, any other plasmid or vector may be used as long as it is replicable and viable in the host.

5           b. Bacteriophage vectors.

There are a number of well known bacteriophage-derived vectors useful according to the invention. Foremost among these are the lambda-based vectors, such as Lambda Zap II or Lambda-Zap Express vectors (Stratagene) that allow inducible expression of the polypeptide encoded by the insert. Others include filamentous bacteriophage such as the M13-based family  
10 of vectors.

c. Viral vectors.

A number of different viral vectors are useful according to the invention, and any viral vector that permits the introduction and expression of one or more of the polynucleotides of the invention in cells is acceptable for use in the methods of the invention. Viral vectors that can be  
15 used to deliver foreign nucleic acid into cells include but are not limited to retroviral vectors, adenoviral vectors, adeno-associated viral vectors, herpesviral vectors, and Semliki forest viral (alphaviral) vectors. Defective retroviruses are well characterized for use in gene transfer (for a review see Miller, A.D. (1990) *Blood* 76:271). Protocols for producing recombinant retroviruses and for infecting cells *in vitro* or *in vivo* with such viruses can be found in Current Protocols in  
20 Molecular Biology, Ausubel, F.M. et al. (eds.) Greene Publishing Associates, (1989), Sections 9.10-9.14, and other standard laboratory manuals.

In addition to retroviral vectors, Adenovirus can be manipulated such that it encodes and expresses a gene product of interest but is inactivated in terms of its ability to replicate in a normal lytic viral life cycle (see for example Berkner et al., 1988, *BioTechniques* 6:616;  
25 Rosenfeld et al., 1991, *Science* 252:431-434; and Rosenfeld et al., 1992, *Cell* 68:143-155). Suitable adenoviral vectors derived from the adenovirus strain Ad type 5 dl324 or other strains of adenovirus (e.g., Ad2, Ad3, Ad7 etc.) are well known to those skilled in the art. Adeno-associated virus (AAV) is a naturally occurring defective virus that requires another virus, such as an adenovirus or a herpes virus, as a helper virus for efficient replication and a  
30 productive life cycle. (For a review see Muzyczka et al., 1992, *Curr. Topics in Micro. and Immunol.* 158:97-129). An AAV vector such as that described in Traschin et al. (1985, *Mol.*



Cell. Biol. 5:3251-3260) can be used to introduce nucleic acid into cells. A variety of nucleic acids have been introduced into different cell types using AAV vectors. (see, for example, Hermonat et al., 1984, Proc. Natl. Acad. Sci. USA 81: 6466-6470; and Traschin et al., 1985, Mol. Cell. Biol. 4: 2072-2081).

5        *Host cells*

Any cell into which a recombinant vector carrying a gene of interest (e.g., a sequence encoding Reg1 $\alpha$ ) may be introduced and wherein the vector is permitted to drive the expression of the peptide encoded by the differentially expressed sequence is useful according to the invention. Any cell in which a differentially expressed molecule of the invention may be  
10    expressed and preferably detected is a suitable host, wherein the host cell is preferably a mammalian cell and more preferably a human cell. Vectors suitable for the introduction of nucleic acid sequences to host cells from a variety of different organisms, both prokaryotic and eukaryotic, are described herein above or known to those skilled in the art.

Host cells may be prokaryotic, such as any of a number of bacterial strains, or may be  
15    eukaryotic, such as yeast or other fungal cells, insect or amphibian cells, or mammalian cells including, for example, rodent, simian or human cells. Cells may be primary cultured cells, for example, primary human fibroblasts or keratinocytes, or may be an established cell line, such as NIH3T3, 293T or CHO cells. Further, mammalian cells useful in the present invention may be phenotypically normal or oncogenically transformed. It is assumed that one skilled in the art can  
20    readily establish and maintain a chosen host cell type in culture.

*Introduction of vectors to host cells.*

Vectors useful in the present invention may be introduced to selected host cells by any of a number of suitable methods known to those skilled in the art. For example, vector constructs may be introduced to appropriate bacterial cells by infection, in the case of E. coli bacteriophage  
25    vector particles such as lambda or M13, or by any of a number of transformation methods for plasmid vectors or for bacteriophage DNA. For example, standard calcium-chloride-mediated bacterial transformation is still commonly used to introduce naked DNA to bacteria (Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY), but electroporation may also be used (Ausubel et al., 1988, Current  
30    Protocols in Molecular Biology, (John Wiley & Sons, Inc., NY, NY)).

For the introduction of vector constructs to yeast or other fungal cells, chemical transformation methods are generally used (e.g. as described by Rose et al., 1990, Methods in Yeast Genetics, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY). For transformation of *S. cerevisiae*, for example, the cells are treated with lithium acetate to achieve transformation efficiencies of approximately  $10^4$  colony-forming units (transformed cells)/ $\mu\text{g}$  of DNA. Transformed cells are then isolated on selective media appropriate to the selectable marker used. Alternatively, or in addition, plates or filters lifted from plates may be scanned for GFP fluorescence to identify transformed clones.

For the introduction of vectors comprising a sequence of interest to mammalian cells, the method used will depend upon the form of the vector. Plasmid vectors may be introduced by any of a number of transfection methods, including, for example, lipid-mediated transfection ("lipofection"), DEAB-dextran-mediated transfection, electroporation or calcium phosphate precipitation. These methods are detailed, for example, in *Current Protocols in Molecular Biology* (Ausubel et al., 1988, John Wiley & Sons, Inc., NY, NY).

Lipofection reagents and methods suitable for transient transfection of a wide variety of transformed and non-transformed or primary cells are widely available, making lipofection an attractive method of introducing constructs to eukaryotic, and particularly mammalian cells in culture. For example, LipofectAMINE<sup>TM</sup> (Life Technologies) or LipoTaxi<sup>TM</sup> (Stratagene) kits are available. Other companies offering reagents and methods for lipofection include Bio-Rad Laboratories, CLONTECH, Glen Research, InVitrogen, JBL Scientific, MBI Fermentas, PanVera, Promega, Quantum Biotechnologies, Sigma-Aldrich, and Wako Chemicals USA.

Following transfection with a vector of the invention, eukaryotic (e.g., human) cells successfully incorporating the construct (intra- or extrachromosomally) may be selected, as noted above, by either treatment of the transfected population with a selection agent, such as an antibiotic whose resistance gene is encoded by the vector, or by direct screening using, for example, FACS of the cell population or fluorescence scanning of adherent cultures. Frequently, both types of screening may be used, wherein a negative selection is used to enrich for cells taking up the construct and FACS or fluorescence scanning is used to further enrich for cells expressing differentially expressed polynucleotides or to identify specific clones of cells, respectively. For example, a negative selection with the neomycin analog G418 (Life Technologies, Inc.) may be used to identify cells that have received the vector, and fluorescence

scanning may be used to identify those cells or clones of cells that express the vector construct to the greatest extent.

### Reg1 $\alpha$ and TIMP1 Polypeptides

The present invention provides a method for the detection of colorectal cancer in an individual by detecting the presence of Reg1 $\alpha$  or TIMP1 in a clinical sample from an individual. In addition the invention encompasses the detection of cancer by identifying Reg1 $\alpha$  or TIMP1 gene product in colon tissue or cells. Alternatively, the invention relates to a method for the detection of colorectal cancer in an individual wherein colorectal cancer is identified by detecting the presence of Reg1 $\alpha$  or TIMP1 and at least one additional colorectal cancer associated marker in the clinical sample from an individual. Polypeptides of the present invention, the detection of which is indicative of colorectal cancer include those having the sequence shown in one or more of SEQ ID Nos. 2, 4, or 100, or alternatively, which are encoded by one or more of SEQ ID Nos. 1, 3 or 33.

Preferred polypeptides which can be detected and are thus indicative of colorectal cancer in an individual are those that are encoded by nucleic acid sequences at least about 70%, 75%, 80%, 90%, 95%, 97%, or 98% identical to a mRNA sequence complementary to the nucleic acid sequence of SEQ ID Nos. 1, 3 or 33. Particularly preferred polypeptides are those of SEQ ID Nos. 2, 4, or 99, or fragments thereof, or polypeptide sequences which are at least about 70%, 75%, 80%, 90%, 95%, 98% or 99% identical in sequence to the amino acid sequence of one or more of SEQ ID Nos. 2, 4, or 100.

In addition to a method for detecting colorectal cancer by identifying the presence of the Reg1 $\alpha$  or TIMP1 polypeptide in a clinical sample from an individual, the invention further comprises a method of detecting cancer by identifying the presence of Reg1 $\alpha$  or TIMP1 in addition to at least one other colorectal cancer associated marker in the same sample (e.g., in the same serum, tissue, or cell sample).

### *Antibodies*

The invention provides a method for colorectal cancer detection comprising the step of detecting the presence of Reg1 $\alpha$  or TIMP1 (and optionally, at least one additional colorectal cancer associated marker) in a clinical sample from an individual. In one embodiment, the presence of Reg1 $\alpha$  or TIMP1, or other marker, in such a sample is detected using a polypeptide

ligand which is preferably detectably labeled, and is capable of binding to Reg1 $\alpha$  or TIMP1, and if present, the other marker, in the sample. In a preferred embodiment, the polypeptide ligand is an antibody. Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized, or chimeric antibodies, single chain antibodies, Fab fragments, Fv fragments F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic antibodies, or other epitope binding polypeptide. Preferably, an antibody, useful in the present invention for the detection of Reg1 $\alpha$  or TIMP1 (and optionally at least one additional colorectal cancer associated marker), is a human antibody or fragment thereof, including scFv, Fab, Fab', F(ab'), Fd, single chain antibody, or Fv. Antibodies, useful in the invention may include a complete heavy or light chain constant region, or a portion thereof, or an absence thereof. An antibody, useful in the invention, may be obtained from an art recognized host, such as rabbit, mouse, rat, donkey, sheep, goat, guinea pig, camel, horse, or chicken. In one embodiment, an antibody, useful in the invention can be a humanized antibody, in which amino acids have been replaced in the non-antigen binding regions in order to more closely resemble a human antibody, while still retaining the original binding ability. Methods for making humanized antibodies are described in Teng et al., 1983, *Proc. Natl. Acad. Sci. USA* 80: 7308-7312; Kozbor et al., 1983, *Immunology Today* 4: 7279; Olsson et al., 1982, *Meth. Enzymol.* 92: 3-16; WO 92/06193; EP 0239400.

Antibodies of the present invention may be monospecific, dispecific, trispecific, or of greater multispecificity. As such, Reg1 $\alpha$  or TIMP1 and optionally an additional colorectal cancer associated marker useful for the detection of colorectal cancer may be detected with separate antibodies, or may be detected with the same antibody. Alternatively, a multispecific antibody may exhibit different specificities for different epitopes on the same protein (e.g., different epitopes on Reg1 $\alpha$ ). While specificity of an antibody useful in the present invention to either Reg1 $\alpha$  or one or more additional colorectal cancer associated markers is preferred, antibodies that bind polypeptides with at least 95%, 90%, 85%, 75%, 65%, 55%, and at least 50% identity to a polypeptide useful in the present invention for the detection of colorectal cancer (i.e., Reg1 $\alpha$ , and/or an additional colorectal cancer associated marker) are also included in the present invention. Also encompassed in the present invention are antibodies which bind to polypeptide molecules which are encoded by one or more nucleic acid sequences which are complementary to, or hybridize to the sequences of SEQ ID Nos. 1, 3 or 33, or one or more sequences which are complementary to, or hybridize to a nucleic acid sequence which encodes an additional colorectal cancer associated marker as described herein.

Antibodies of the present invention which are useful for the detection of colorectal cancer may further act as agonists or antagonists of the activity of the polypeptide molecules to which they bind, and may thus be useful as therapeutic molecules for the treatment or prevention of colorectal cancer.

5        An important, but not limiting, role of an antibody of the present invention is to provide for the purification, or detection of Reg1 $\alpha$  or TIMP1 or other colorectal cancer associated markers in a patient sample, including both in vitro and in vivo detection methods. Antibodies useful for the detection of colorectal cancer as described herein do not have to be used alone, and can be fused to other polypeptides, including a heterologous polypeptide at the N- or C-terminus  
10 of the antibody polypeptide sequence. For example, an antibody useful in the present invention may be fused with a detectable label to facilitate detection of the antibody when bound to a target polypeptide. Methods for detectably labeling an antibody polypeptide are known to those of skill in the art.

For the production of antibodies useful in the present invention, various hosts including  
15 goats, rabbits, rats, mice, etc., may be immunized by injection with the protein products (or any portion, fragment, or oligonucleotide thereof which retains immunogenic properties) of the candidate genes of the invention. Depending on the host species, various adjuvants may be used to increase the immunological response. Such adjuvants include but are not limited to Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin,  
20 pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol. BCG (bacilli Calmette-Guerin) and *Corynebacterium parvum* are potentially useful human adjuvants.

Polyclonal antisera or monoclonal antibodies can be made using methods known in the art. A mammal such as a mouse, hamster, or rabbit, can be immunized with an immunogenic  
25 form of a Reg1 $\alpha$  or TIMP1 polypeptide, fragment, modified form thereof, or variant form thereof. Alternatively, an animal may be immunized with an immunogenic form of one or more additional colorectal cancer associated marker polypeptides. Techniques for conferring immunogenicity on such molecules include conjugation to carriers or other techniques well known in the art. For example, the immunogenic molecule can be administered in the presence  
30 of adjuvant as described above. Immunization can be monitored by detection of antibody titers in plasma or serum. Standard immunoassay procedures can be used with the immunogen as

antigen to assess the levels and the specificity of antibodies. Following immunization, antisera can be obtained and, if desired, polyclonal antibodies isolated from the sera.

To produce monoclonal antibodies, antibody producing cells (lymphocytes) can be harvested from an immunized animal and fused with myeloma cells by standard somatic cell fusion procedures thus immortalizing these cells and yielding hybridoma cells. Such techniques are well known in the art (see, e.g., Kohler and Milstein, 1975, *Nature* 256: 495-497; Kozbor et al., 1983, *Immunol. Today* 4: 72, Cole et al., 1985, In *Monoclonal Antibodies in Cancer Therapy*, Allen R. Bliss, Inc., pages 77-96). Additionally, techniques described for the production of single-chain antibodies (U.S. Patent No. 4,946,778) can be adapted to produce antibodies according to the invention.

Antibody fragments which can specifically bind to a polypeptide of the invention such as Reg1 $\alpha$  or TIMP1 or other colorectal cancer associated marker polypeptides, fragments thereof, modified forms thereof, and variants thereof, also may be generated by known techniques. For example, such fragments include, but are not limited to, F(ab')<sub>2</sub> fragments which can be produced by pepsin digestion of the antibody molecule and the Fab fragments which can be generated by reducing the disulfide bridges of the F(ab')<sub>2</sub> fragments. VH regions and FV regions can be expressed in bacteria using phage expression libraries (e.g., Ward et al., 1989, *Nature* 341: 544-546; Huse et al., 1989, *Science* 246: 1275-1281; McCafferty et al., 1990, *Nature* 348: 552-554).

Chimeric antibodies, i.e., antibody molecules that combine a non-human animal variable region and a human constant region also are within the scope of the invention. Chimeric antibody molecules include, for example, the antigen binding domain from an antibody of a mouse, rat, or other species, with human constant regions. Standard methods may be used to make chimeric antibodies containing the immunoglobulin variable region which recognizes the gene product of Reg1 $\alpha$  antigens of the invention (see, e.g., Morrison et al., 1985, *Proc. Natl. Acad. Sci. USA* 81: 6851; Takeda et al., 1985, *Nature* 314: 452; U.S. Patent No. 4,816,567; U.S. Patent No. 4,816,397).

#### Other Colorectal cancer Specific Analysis

In addition to the detection of colorectal cancer by identifying expression of Reg1 $\alpha$  or TIMP1, or detecting Reg1 $\alpha$  or TIMP1 polypeptides, the present invention further comprises a method for detecting colorectal cancer wherein a nucleic acid molecule encoding Reg1 $\alpha$  or TIMP1, or Reg1 $\alpha$  or TIMP1 polypeptide is identified in combination with at least one other

nucleic acid sequence encoding a known colorectal cancer associated marker in a clinical sample from an individual. Alternatively, the presence of Reg1 $\alpha$  or TIMP1 is detected in combination with at least one additional colorectal cancer marker amino acid sequence. Similar to the methods described above for Reg1 $\alpha$ , a nucleic acid molecule which encodes at least one other colorectal cancer associated marker may be used to generate a nucleic acid probe for detection of the colorectal cancer associated marker sequence in a patient sample, or may be used to generate amplification primers to amplify the colorectal cancer associated marker sequence from a patient sample comprising the sequence, thus identifying the presence of the colorectal cancer associated marker in the sample, and thus indicating the detection of colorectal cancer. A colorectal cancer associated marker polypeptide sequence may be used, as described above for Reg1 $\alpha$  to generate antibodies useful for detection of the colorectal cancer associated marker in a clinical sample. Methods for detecting a colorectal cancer associated marker nucleic acid or amino acid sequence are described below, and may be adapted from the methods for the detection of Reg1 $\alpha$  nucleic acid or amino acid in a clinical sample.

15 A "colorectal cancer associated marker" useful in the present invention, refers to a polypeptide or nucleic acid sequence which exhibits over- or underexpression of at least 10% in colorectal cancer cells, tissue, or serum obtained from an individual having colorectal cancer, relative to the level of expression in cells, tissue, or serum obtained from an individual that does not have colorectal cancer. Non-limiting examples of colorectal cancer associated markers useful in the present invention include the nucleic acid molecules of SEQ ID Nos 1, 3, 5-71, and/or the polypeptide molecules of SEQ ID Nos 2, 4, 72-138. In one embodiment, the polypeptide sequences of SEQ ID Nos 2, 4, 72-138 are encoded by the nucleic acid sequences of 1, 3, 5-71, respectively. It will be appreciated by one of skill in the art that, where the method of the invention relates to detection of Reg1 $\alpha$  and at least one other colorectal cancer associated marker, TIMP1 may be included as a potential "other colorectal cancer associated marker". Likewise, where the detection method is based on the detection of TIMP1 and at least one other colorectal cancer associated marker, Reg1 $\alpha$  may be included as a potential "other colorectal cancer associated marker". Alternatively, a colorectal cancer associated marker, as used in the present invention, may refer to a carbohydrate epitope present on a polypeptide or nucleic acid molecule and/or an antibody molecule which recognizes and is capable of binding to such an epitope, wherein the carbohydrate epitope is known to be associated with the presence of colorectal cancer in an individual. Such carbohydrate epitopes may be present on more than one unrelated protein or polypeptide. In one embodiment, such a carbohydrate epitope is CA 19-9,

also known as sialyl-Lewis<sup>a</sup>, is a tumor marker defined by a monoclonal antibody as a carbohydrate epitope, related to the blood group antigens, composed of a branching, 5-sugar structure covalently bound to a variety of glycoproteins or glycolipids. The proteins primarily belong to the mucin family and the lipids are usually membrane associated. The CA 19-9 epitope is typically the terminal moiety of a complex, O-linked carbohydrate structure on either macromolecule. Other tumor markers also defined as various carbohydrate epitopes useful in the present invention as a "colorectal cancer associated marker" include CA72-4 which is indicative of the presence of the Tag 72 antigen, which is a triply sialylated Tn antigen on varying protein backbones; Thomsen Freidenreich antigen (TF), which is a sialylated n-acetyl galactosamine moiety O-linked to various peptides; Tn and sialylated Tn (sTn) which is the backbone of the TF antigen without the terminal n-acetyl galactosamine moiety, O-linked to various peptides; CA 50 which is an epitope corresponding to sialylated Lewis A blood group antigen; CA 549 which is a CHO moiety on muc-1; CA 242 which is a sialylated CHO; LASA which is a lipid associated sialic acid, that is, a lipid without a protein associated to it; Du-PAN's 1-5, which are pancreatic associated mucin-like CHO antigens. These useful colon cancer specific antigens and others are known in the art and are described, for example, in "Serological Cancer Markers" Sell, S., Ed. 1992. Humana Press Inc., Totowa, NJ.

Table 1 below shows a list of "colorectal cancer associated markers" useful in the invention (although colorectal cancer associated markers useful in the invention are not limited to those shown in Table 1), and their correspondence with the sequences set forth in the "Sequence listing".

Table 1

SEQ ID NO	Gene Symbol	Length	Type	SEQ ID NO	Gene Symbol	Length	Type
5	CEACAM5	2974	DNA	72	CEACAM5	702	Protein
6	AFP	2032	DNA	73	AFP	609	Protein
7	IL8	1639	DNA	74	IL8	99	Protein
8	SPP1	1524	DNA	75	SPP1	300	Protein
9	KIAA1077	5500	DNA	76	KIAA1077	871	Protein
10	MMP12	1778	DNA	77	MMP12	470	Protein



11	UBD	777	DNA	78	UBD	165	Protein
12	COL1A1	5921	DNA	79	COL1A1	1464	Protein
13	LUM	1804	DNA	80	LUM	338	Protein
14	ENC1	4827	DNA	81	ENC1	589	Protein
15	PIGPC1	1098	DNA	82	PIGPC1	193	Protein
16	GTF3A	1381	DNA	83	GTF3A	423	Protein
17	CTSB	1978	DNA	84	CTSB	339	Protein
18	MCJ	1074	DNA	85	MCJ	150	Protein
19	SLC12A2	4098	DNA	86	SLC12A2	1212	Protein
20	C20orf42	3120	DNA	87	C20orf42	230	Protein
21	SDBCAG84	1337	DNA	88	SDBCAG84	383	Protein
22	NAP1L1	2908	DNA	89	NAP1L1	391	Protein
23	OSF-2	3213	DNA	90	OSF-2	836	Protein
24	COL6A3	10558	DNA	91	COL6A3	3176	Protein
25	SPARC	2133	DNA	92	SPARC	303	Protein
26	TGFBI	2691	DNA	93	TGFBI	683	Protein
27	FN1	8027	DNA	94	FN1	2355	Protein
28	COL1A2	5084	DNA	95	COL1A2	1366	Protein
29	S100A11	595	DNA	96	S100A11	105	Protein
30	LC27	2116	DNA	97	LC27	283	Protein
31	IRAK1	3583	DNA	98	IRAK1	712	Protein
32	IFITM2	905	DNA	99	IFITM2	132	Protein
33	TIMP1	782	DNA	100	TIMP1	207	Protein
34	IGFBP7	1124	DNA	101	IGFBP7	282	Protein
35	IFITM1	647	DNA	102	IFITM1	125	Protein
36	COL3A1	5489	DNA	103	COL3A1	1466	Protein

37	IGFBP5	1722	DNA	104	IGFBP5	272	Protein
38	RegIV	1200	DNA	105	RegIV	158	Protein
39	AGR2	1701	DNA	106	AGR2	175	Protein
40	HSPCA	2259	DNA	107	HSPCA	732	Protein
41	KIAA1199	7080	DNA	108	KIAA1199	1361	Protein
42	MMP1	1973	DNA	109	MMP1	469	Protein
43	MMP7	1127	DNA	110	MMP7	267	Protein
44	TSC	1163	DNA	111	TSC	216	Protein
45	HAIK1	2007	DNA	112	HAIK1	422	Protein
46	DAP3	1650	DNA	113	DAP3	398	Protein
47		2566	DNA	114		75	Protein
48		2067	DNA	115		163	Protein
49	KRT8	1752	DNA	116	KRT8	483	Protein
50	KRT18	1412	DNA	117	KRT18	430	Protein
51	KRT19	1407	DNA	118	KRT19	400	Protein
52	KRT20	1723	DNA	119	KRT20	424	Protein
53	MUC1	4139	DNA	120	MUC1	1255	Protein
54	MUC2	15720	DNA	121	MUC2	5179	Protein
55	MUC3	4707	DNA	122	MUC3	1217	Protein
56	MUC5AC	4151	DNA	123	MUC5AC	1373	Protein
57	CGB5	880	DNA	124	CGB5	165	Protein
58	EGFR	5532	DNA	125	EGFR	1210	Protein
59	ERBB2	4530	DNA	126	ERBB2	1255	Protein
60	FTH1	801	DNA	127	FTH1	190	Protein
61	FTL	878	DNA	128	FTL	175	Protein
62	ALPP	2747	DNA	129	ALPP	535	Protein

63	ODC1	2062	DNA	130	ODC1	461	Protein
64	MUC16	3557	DNA	131	MUC16	1148	Protein
65	CEACAM1	3464	DNA	132	CEACAM1	526	Protein
66	CEACAM3	1022	DNA	133	CEACAM3	212	Protein
67	CEACAM4	1190	DNA	134	CEACAM4	244	Protein
68	CEACAM6	2249	DNA	135	CEACAM6	344	Protein
69	CEACAM7	2292	DNA	136	CEACAM7	265	Protein
70	CEACAM8	2297	DNA	137	CEACAM8	349	Protein
71	CA9	1552	DNA	138	CA9	459	Protein

#### Detection Assays

The present invention provides method for detecting colorectal cancer, or alternatively, determining whether a subject is at risk for developing colorectal cancer by detecting the disclosed biomarkers (i.e., the nucleic acid sequence of Reg1 $\alpha$  or TIMP1 and optionally, one or more nucleic acid sequences encoding an additional colorectal cancer associated marker and/or polypeptide markers such as Reg1 $\alpha$  or TIMP1 and optionally, at least one additional colorectal cancer associated marker) for the disease or condition encoded thereby.

In clinical applications, human tissue samples, preferably serum, can be screened for the presence and/or absence of Reg1 $\alpha$  or TIMP1 and/or other colorectal cancer associated markers identified herein. Such samples may comprise tissue samples, whole cells, cell lysates, or isolated nucleic acids, including, for example, needle biopsy cores, surgical resection samples, lymph node tissue, or serum. A sample for analysis as described herein is preferably a serum sample. A serum sample may be obtained from an individual using methods which are well known to those of skill in the art. Briefly, a whole venous or arterial blood sample from an individual is collected into a test tube. The whole blood sample is permitted to incubate at room temperature for approximately 15-30 to allow the blood to clot. Once clotted, the sample is centrifuged at approximately 1500 to 3000 rpm for 5-30 minutes to completely separate the serum from the cellular components. This centrifugation may be repeated if necessary to achieve complete separation. The resulting serum sample may be subsequently screened for the presence

of Reg1 $\alpha$  nucleic acid or amino acid and/or one or more additional colorectal cancer associated markers as described herein.

#### *Screening for nucleic acid molecules*

In one embodiment, the detection method of the present invention comprises determining  
5 whether a clinical sample from an individual contains mRNA of a colorectal cancer associated marker, preferably Reg1 $\alpha$  or TIMP1, but also optionally including additional colorectal cancer associated markers as described herein. Techniques for determining the presence of a nucleic acid molecule of interest include Northern blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), in situ hybridization, PCR, and quantitative amplification.

10 Prior to detection of target nucleic acid molecules in a clinical sample, it is preferred to first isolate the mRNA from the sample to facilitate detection of the target sequence (i.e., a sequence encoding Reg1 $\alpha$  or TIMP1). Methods for isolation of mRNA from a biological sample are well known in the art. Briefly, where the sample is a serum sample, for example, 0.1 ml of 2 M sodium acetate, pH 4, 1 ml water-saturated phenol, and 0.2 ml of 49:1 chloroform/isoamyl  
15 alcohol are added to the serum sample sequentially. The sample is mixed after the addition of each component, and incubated for 15 min at 0-4°C after all components have been added. The sample is separated by centrifugation for 20 min at 10,000 x g, 4°C, precipitated by the addition of 1 ml of 100% isopropanol, incubated for 30 minutes at -20°C and pelleted by centrifugation for 10 minutes at 10,000 x g, 4°C. The resulting RNA pellet is dissolved in 0.3 ml denaturing  
20 solution, transferred to a microfuge tube, precipitated by the addition of 0.3 ml of 100% isopropanol for 30 minutes at -20°C, and centrifuged for 10 minutes at 10,000 x g at 4°C. The RNA pellet is washed in 70% ethanol, dried, and resuspended in 100-200 $\mu$ l DEPC-treated water or DEPC-treated 0.5% SDS (Chomczynski and Sacchi, 1987, Anal. Biochem., 162: 156).

Alternatively, total RNA may be extracted from a clinical sample according to the present  
25 invention using a commercially available RNA isolation reagent such as Trizol (Invitrogen, Carlsbad, CA), following the manufacturers instructions. Purity and integrity of RNA is assessed by absorbance at 260/280 nm and separation of RNA samples on a 1% agarose gel followed by inspection under ultraviolet light.

Following mRNA isolation, the mRNA may be reverse transcribed to provide a cDNA  
30 sample according to methods well known to those of skill in the art (see, e.g., Ausubel et al. (1995), Short Protocols in Molecular Biology, 3<sup>rd</sup> Ed. John Wiley and Sons, Inc.)

Accordingly, in one aspect, the invention provides probes and primers that specifically hybridize to the Reg1 $\alpha$  or TIMP1 nucleic acid sequences disclosed herein, or which can hybridize to a nucleic acid molecule encoding an additional colorectal cancer associated marker as described herein. Accordingly, the nucleic acid probes comprise a region of a nucleic acid sequence of SEQ ID Nos 1, 3, or 33 sufficient to hybridize with a nucleic acid substantially complementary to the sequence of SEQ ID Nos 1, 3 or 33. Preferred nucleic acid molecules for use as probes/primers can further comprise a region of nucleic acid sequence substantially complementary to the sequence of SEQ ID Nos. 1, 3 or 33 sufficient to hybridize with the sequence of SEQ ID Nos. 1, 3 or 33. In addition, nucleic acid sequences useful as probes/primers comprise a nucleotide sequence at least about 8 nucleotides in length, at least about 12 nucleotides in length, preferably at least about 15 nucleotides, more preferably about 25 nucleotides, and most preferably at least 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a portion of the coding sequence of a marker nucleic acid sequence, which nucleic acid sequence is represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto.

In one embodiment, the method comprises using a nucleic acid probe to determine the presence of a Reg1 $\alpha$  or TIMP1 nucleic acid molecule in a clinical sample (such as a serum sample or a nucleic acid sample extracted therefrom). Specifically, the method comprises:

1. Providing a nucleic acid probe comprising a nucleotide sequence at least about 8 nucleotides in length, at least about 12 nucleotides in length, preferably at least about 15 nucleotides, more preferably about 25 nucleotides, and most preferably at least about 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a portion of the coding sequence of a nucleic acid sequence represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto;
2. Obtaining a clinical sample from a patient potentially comprising a Reg1 $\alpha$  or TIMP1 nucleic acid sequence;
3. Providing a second clinical sample from an individual known to not have colorectal cancer;

4. Contacting the nucleic acid probe under stringent conditions with RNA of each of said first and second clinical samples (e.g., in a Northern blot or *in situ* hybridization assay); and
5. Comparing (a) the amount of hybridization of the probe with RNA of the first serum sample, with (b) the amount of hybridization of the probe with RNA of the second clinical sample; wherein a statistically significant difference in the amount of hybridization with the RNA of the first clinical sample as compared to the amount of hybridization with the RNA of the second clinical sample is indicative of the presence of Reg1 $\alpha$  or TIMP1 in the first clinical sample.

10 Although, primarily drawn to detection of Reg1 $\alpha$  or TIMP1 in a clinical sample such as serum, in one aspect, the present invention provides a method comprising *in situ* hybridization detection of Reg1 $\alpha$  or TIMP1 with a probe derived from a nucleic acid sequence represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto. Preferably, the hybridization probe is detectably labeled. The method comprises contacting the labeled hybridization probe  
15 with a tissue or cell sample from an individual suspected of having colorectal cancer, washing off any unbound probe, and detecting the signal produced by the detectable label, wherein the detection of the detectable signal is indicative of the presence of Reg1 $\alpha$  or TIMP1 in the sample, and thus permits the detection of colorectal cancer. Alternatively, the tissue or cell is additionally hybridized with a detectably labeled nucleic acid probe which is capable of  
20 specifically hybridizing with a nucleic acid sequence that encodes at least one additional colorectal cancer associated marker. Detection of the second detectably labeled probe is thus indicative of the presence of the additional colorectal cancer associated marker in the sample, and in conjunction with the detection of Reg1 $\alpha$  or TIMP1, permits the detection of colorectal cancer in the individual. Specific methods for *in situ* hybridization are well known in the art.

25 Alternatively, methods such as PCR, Northern analysis, and Taqman may be used to detect and/or quantitate the expression of a nucleic acid sequence encoding Reg1 $\alpha$  in a clinical sample. In one embodiment, reverse transcription PCR (RT-PCR) is performed using primers designed to specifically hybridize to a predetermined portion of the Reg1 $\alpha$  mRNA sequence isolated from a clinical sample. Generation of a PCR product by such a reaction is thus  
30 indicative of the presence of the Reg1 $\alpha$  or TIMP1 sequence in the sample. The technique of designing primers for PCR amplification is well known in the art. Oligonucleotide primers and probes are 5 to 100 nucleotides in length, ideally from 17 to 40 nucleotides, although primers and

probes of different length are of use. Primers for amplification are preferably about 17 -25 nucleotides. Primers useful according to the invention are also designed to have a particular melting temperature ( $T_m$ ) by the method of melting temperature estimation. Commercial programs, including Oligo™ (MBI, Cascade, CO), Primer Design and programs available on the internet, including Primer3 and Oligo Calculator can be used to calculate a  $T_m$  of a nucleic acid sequence useful according to the invention. Preferably, the  $T_m$  of an amplification primer useful according to the invention, as calculated for example by Oligo Calculator, is preferably between about 45 and 65° C and more preferably between about 50 and 60° C. Preferably, the  $T_m$  of a probe useful according to the invention is 7° C higher than the  $T_m$  of the corresponding amplification primers. It is preferred that, following generation of cDNA by RT-PCR, the cDNA fragment is cloned into an appropriate sequencing vector, such as a PCRII vector (TA cloning kit; Invitrogen). The identity of each cloned fragment is then confirmed by sequencing in both directions. It is expected that the sequence obtained from sequencing would be the same as the known sequence of Reg1 $\alpha$  to TIMP1 as described herein.

Alternatively, the presence of an mRNA sequence encoding Reg1 $\alpha$  or TIMP1 may be detected by Northern analysis. Sequence confirmed cDNAs, that is, cDNAs encoding Reg1 $\alpha$  or TIMP1 (or alternatively an additional colorectal cancer associated marker) are used to produce <sup>32</sup>P-labeled cDNA probes using techniques well known in the art (see, for example, Ausubel, *supra*). Labeled probes for Northern analysis may also be produced using commercially available kits (Prime-It Kit, Stratagene, La Jolla, CA). Northern analysis of total RNA obtained from a clinical sample may be performed using classically described techniques. For example, total RNA samples are denatured with formaldehyde / formamide and run for two hours in a 1% agarose, MOPS-acetate-EDTA gel. RNA is then transferred to nitrocellulose membrane by upward capillary action and fixed by UV cross-linkage. Membranes are pre-hybridized for at least 90 minutes and hybridized overnight at 42° C. Post hybridization washes are performed as known in the art (Ausubel, *supra*). The membrane is then exposed to x-ray film overnight with an intensifying screen at -80° C. Labeled membranes are then visualized after exposure to film. The signal produced on the x-ray film by the radiolabeled cDNA probes can then be quantified using any technique known in the art, such as scanning the film and quantifying the relative pixel intensity using a computer program such as NIH Image (National Institutes of Health, Bethesda, MD), wherein the detection of hybridization of a Reg1 $\alpha$ -specific probe to the clinical sample is indicative of the presence of Reg1 $\alpha$  or TIMP1 and thus may be used to detect colorectal cancer.

In an alternate embodiment, the presence and optionally the quantity of Reg1 $\alpha$  or TIMP1 in a clinical sample may be determined using the Taqman<sup>TM</sup> (Perkin-Elmer, Foster City, CA) technique, which is performed with a transcript-specific antisense probe (i.e., a probe capable of specifically hybridizing to Reg1 $\alpha$ ). This probe is specific for a Reg1 $\alpha$  or TIMP1 PCR product and is prepared with a quencher and fluorescent reporter probe complexed to the 5' end of the oligonucleotide. Different fluorescent markers can be attached to different reporters, allowing for measurement of two products in one reaction (e.g., measurement of Reg1 $\alpha$  or TIMP1 and at least one additional colorectal cancer associated marker). When Taq DNA polymerase is activated, it cleaves off the fluorescent reporters by its 5'-to-3' nucleolytic activity. The reporters, now free of the quenchers, fluoresce. The color change is proportional to the amount of each specific product and is measured by fluorometer, therefore, the amount of each color can be measured and the RT-PCR product can be quantified. The PCR reactions can be performed in 96 well plates so that samples derived from many individuals can be processed and measured simultaneously. The Taqman<sup>TM</sup> system has the additional advantage of not requiring gel electrophoresis and allows for quantification when used with a standard curve.

#### *Screening for polypeptide molecules*

The Reg1 $\alpha$ - or TIMP1-specific and colorectal cancer marker-specific antibodies described above may be used to detect the presence of Reg1 $\alpha$  or TIMP1 or an additional colorectal cancer associated marker in a clinical sample by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitation reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e. g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasyllol) supplemented with protein phosphatase and/or protease inhibitors (e. g., EDTA, PMSF, aprotinin, sodium vanadate), adding



the antibody of interest to the cell lysate, incubating for a period of time (e. g., 1-4 hours) at 4 C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4 C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. In the case of immunoprecipitation of a serum sample, however the above protocol is  
5 carried out absent the cell lysis step. The ability of the antibody to immunoprecipitate Reg1 $\alpha$  or TIMP1 (or other colorectal cancer marker) antigen can be assessed by, e. g., western blot analysis. The parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e. g., preclearing the cell lysate with sepharose beads) are well known to those of skill in the art (Ausubel et al, *supra*).

10 Reg1 $\alpha$  or TIMP1 polypeptides, and optionally one or more additional colorectal cancer associated markers may be detected in a patient clinical sample using Western blot analysis. Briefly, Western blot analysis comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e. g., 8%-20% SDS-PAGE), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon,  
15 blocking the membrane in blocking solution (e. g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e. g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e. g., an antihuman antibody) conjugated to an enzymatic substrate (e. g., horseradish  
20 peroxidase or alkaline phosphatase) or radioactive molecule (e. g., <sup>32</sup>P or <sup>125</sup>I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. Methods for the optimization of such an analysis are well known in the art (Ausubel, et al., *supra*).

Alternatively, the presence of Reg1 $\alpha$  or TIMP1 and optionally one or more additional  
25 colorectal cancer associated markers in a clinical sample may be detected by ELISA. ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate (or other suitable container) with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e. g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the  
30 antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest, that is, the antibody which will bind to Reg1 $\alpha$  or TIMP1 or a second colorectal cancer associated marker) conjugated to a detectable

compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. This method may be modified or optimized according techniques which are known to those of  
5 skill in the art.

The binding affinity of an antibody to an antigen and the off-rate of an antibodyantigen interaction can be determined by competitive binding assays. One example of such an assay is a radioimmunoassay comprising the incubation of labeled antigen (e. g., Reg1 $\alpha$  labeled with 3H or 125I) with an anti-Reg1 $\alpha$  or TIMP1 antibody in the presence of increasing amounts of unlabeled  
10 antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e. g., 3H or 125I) in the presence of increasing amounts of an  
15 unlabeled second antibody.

Preferably, the above detection assays re be carried out using antibodies to detect the protein product encoded by a nucleic acid having the sequence of SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto. Preferably, the protein product has the sequence of one or more of SEQ ID Nos. 2, 4, or 100. In addition, the above detection assays may be conducted  
20 using one or more antibodies which specifically recognize and bind to at least one additional colorectal cancer associated marker. Accordingly, in one embodiment, the assay would include contacting the proteins of the test cell with an antibody specific for the gene product of a nucleic acid represented by SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto, and determining the approximate amount of immunocomplex formation by the antibody and the  
25 proteins of the test cell, wherein a detection of such an immunocomplex is indicative of the presence of the antigen, and thus, permits the detection of colorectal cancer.

Immunoassays, useful in the present invention include those described above, and can also include both homogeneous and heterogeneous procedures such as fluorescence polarization immunoassay (FPIA), fluorescence immunoassay (FIA), enzyme immunoassay (EIA), and  
30 nephelometric inhibition immunoassay (NIA).

In another embodiment, the level of the encoded product, i.e., the product encoded by SEQ ID Nos 1, 3 or 33, or a sequence complementary thereto, in a biological fluid (e.g., blood or urine) of a patient may be determined as a way of monitoring the level of expression of the marker nucleic acid sequence in cells of that patient. Such a method would include the steps of  
5 obtaining a sample of a biological fluid from the patient, contacting the sample (or proteins from the sample) with an antibody specific for a encoded marker polypeptide, and determining the amount of immune complex formation by the antibody, with the amount of immune complex formation being indicative of the level of the marker encoded product in the sample. This determination is particularly instructive when compared to the amount of immune complex  
10 formation by the same antibody in a control sample taken from a normal individual or in one or more samples previously or subsequently obtained from the same person.

In another embodiment, the method can be used to determine the amount of marker polypeptide present in a cell, which in turn can be correlated with progression of a hyperproliferative disorder, e.g., colorectal cancer. The level of the marker polypeptide can be  
15 used predictively to evaluate whether a sample of cells contains cells which are, or are predisposed towards becoming, transformed cells. Moreover, the subject method can be used to assess the phenotype of cells which are known to be transformed, the phenotyping results being useful in planning a particular therapeutic regimen. For instance, very high levels of the marker polypeptide in sample cells is a powerful diagnostic and prognostic marker for a cancer, such as  
20 colorectal cancer. The observation of marker polypeptide level can be utilized in decisions regarding, e.g., the use of more aggressive therapies.

As set out above, one aspect of the present invention relates to detection assays for determining, in the context of cells isolated from a patient, if the level of a marker polypeptide is significantly reduced in the sample cells. The term "significantly reduced" refers to a cell  
25 phenotype wherein the cell possesses a reduced cellular amount of the marker polypeptide relative to a normal cell of similar tissue origin. For example, a cell may have less than about 50%, 25%, 10%, or 5% of the marker polypeptide that a normal control cell. In particular, the assay evaluates the level of marker polypeptide in the test cells, and, preferably, compares the measured level with marker polypeptide detected in at least one control cell, e.g., a normal cell  
30 and/or a transformed cell of known phenotype.

Of particular importance to the subject invention is the ability to quantitate the level of normal or abnormal Reg1 $\alpha$  or TIMP1 expression. The expression of Reg1 $\alpha$  or TIMP1, and/or

the level of expression of Reg1 $\alpha$  or TIMP1 can be used predictively to evaluate whether a patient is predisposed towards developing colorectal cancer, or for determining the severity of colorectal cancer.

5 In one embodiment, tissue samples may be used to measure Reg1 $\alpha$  or TIMP1 expression by immunohistochemical staining which may be used to determine the number of cells (i.e., colon cells) expressing Reg1 $\alpha$  or TIMP1. For such staining, a multiblock of tissue is taken from the biopsy or other tissue sample and subjected to proteolytic hydrolysis, employing such agents as protease K or pepsin. In certain embodiments, it may be desirable to isolate a nuclear fraction from the sample cells and detect the level of the marker polypeptide in the nuclear fraction.

10 The tissue samples are fixed by treatment with a reagent such as formalin, glutaraldehyde, methanol, or the like. The samples are then incubated with an antibody, preferably a monoclonal antibody, with binding specificity for Reg1 $\alpha$  or TIMP1 and optionally an additional colorectal cancer associated marker. This antibody may be conjugated to a label for subsequent detection of binding. Samples are incubated for a time sufficient for formation of  
15 the immunocomplexes. Binding of the antibody is then detected by virtue of a label conjugated to this antibody. Where the antibody is unlabeled, a second labeled antibody may be employed, e.g., which is specific for the isotype of the anti-marker polypeptide antibody. Examples of labels which may be employed include radionuclides, fluorescers, chemiluminescers, enzymes and the like.

20 Where enzymes are employed, the substrate for the enzyme may be added to the samples to provide a colored or fluorescent product. Examples of suitable enzymes for use in conjugates include horseradish peroxidase, alkaline phosphatase, malate dehydrogenase and the like. Where not commercially available, such antibody-enzyme conjugates are readily produced by techniques known to those skilled in the art. Other assays, known to those of skill in the art for  
25 determining the presence and/or quantity of a polypeptide in a sample (either serum or tissue) are also encompassed by the present invention.

#### Drug screening

Several in vivo methods can be used to identify compounds that modulate expression of Reg1 $\alpha$  or TIMP1 nucleic acids (SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto)  
30 and/or alter for example, inhibit the bioactivity of the encoded polypeptide (e.g., SEQ ID Nos: 2, 4, or 100).

Drug screening is performed by adding a test compound to a sample of cells, and monitoring the effect. A parallel sample which does not receive the test compound is also monitored as a control. The treated and untreated cells are then compared by any suitable phenotypic criteria, including but not limited to microscopic analysis, viability testing, ability to replicate, histological examination, the level of a particular RNA or polypeptide associated with the cells, the level of enzymatic activity expressed by the cells or cell lysates, and the ability of the cells to interact with other cells or compounds. Differences between treated and untreated cells indicates effects attributable to the test compound.

Desirable effects of a test compound include an effect on any phenotype that was conferred by the cancer-associated marker nucleic acid sequence. Examples include a test compound that limits the overabundance of mRNA, limits production of the encoded protein, or limits the functional effect of the protein. The effect of the test compound would be apparent when comparing results between treated and untreated cells.

The invention thus also encompasses methods of screening for agents which inhibit expression of Reg1 $\alpha$  or TIMP1 nucleic acid (SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto) *in vitro*, comprising exposing either a cell or tissue in which Reg1 $\alpha$  or TIMP1 nucleic acid mRNA is detectable or cultured cells comprising and capable of expressing Reg1 $\alpha$  or TIMP1 nucleic acid to an agent in order to determine whether the agent is capable of inhibiting production of the mRNA; and determining the level of mRNA in the exposed cells or tissue, wherein a decrease in the level of the mRNA after exposure of the cell line to the agent is indicative of inhibition of the marker nucleic acid mRNA production.

Alternatively, the screening method may include *in vitro* screening of a cell or tissue in which Reg1 $\alpha$  or TIMP1 is detectable, or cultured cells which express Reg1 $\alpha$  or TIMP1, to an agent suspected of inhibiting production of Reg1 $\alpha$  or TIMP1 protein; and determining the level of the Reg1 $\alpha$  or TIMP1 protein in the cells or tissue, wherein a decrease in the level of marker protein after exposure of the cells or tissue to the agent is indicative of inhibition of marker protein production.

The invention also encompasses *in vivo* methods of screening for agents which inhibit expression of the marker nucleic acids, comprising exposing a mammal having tumor cells or serum in which Reg1 $\alpha$  or TIMP1 mRNA or protein is detectable to an agent suspected of inhibiting production of marker mRNA or protein; and determining the level of marker mRNA

or protein in serum or tumor cells of the exposed mammal. A decrease in the level of marker mRNA or protein after exposure of the mammal to the agent is indicative of inhibition of marker nucleic acid expression. Optionally, the effect of the candidate agent on the expression of at least one additional colorectal cancer associated marker may also be determined.

5           Accordingly, the invention provides a method comprising incubating a cell expressing the marker nucleic acids (SEQ ID Nos: 1, 3 or 33, or a sequence complementary thereto) with a test compound and measuring the mRNA or protein level. The invention further provides a method for quantitatively determining the level of expression of the marker nucleic acids in a cell population or clinical sample, and a method for determining whether an agent is capable of  
10   increasing or decreasing the level of expression of the Reg1 $\alpha$  or TIMP1 nucleic acid in a cell population or clinical sample. The method for determining whether an agent is capable of increasing or decreasing the level of expression of Reg1 $\alpha$  or TIMP1 nucleic acid in a cell population comprises the steps of (a) preparing cell extracts from control and agent-treated cell populations, (b) isolating the Reg1 $\alpha$  or TIMP1 polypeptide from the cell extracts, (c) quantifying  
15   (e.g., in parallel) the amount of an immunocomplex formed between Reg1 $\alpha$  or TIMP1 polypeptide and an antibody specific to said polypeptide. The Reg1 $\alpha$  or TIMP1 polypeptide of this invention may also be quantified by assaying for its bioactivity. Agents that induce an increase in Reg1 $\alpha$  or TIMP1 nucleic acid expression may be identified by their ability to increase the amount of immunocomplex formed in the treated cell as compared with the amount of the  
20   immunocomplex formed in the control cell. In a similar manner, agents that decrease expression of Reg1 $\alpha$  or TIMP1 nucleic acid may be identified by their ability to decrease the amount of the immunocomplex formed in the treated cell extract as compared to the control cell.

mRNA levels can be determined by Northern blot hybridization. mRNA levels can also be determined by methods involving PCR. Other sensitive methods for measuring mRNA, which  
25   can be used in high throughput assays, e.g., a method using a DELFIA endpoint detection and quantification method, are described, e.g., in Webb and Hurskainen (1996) *Journal of Biomolecular Screening* 1:119. Reg1 $\alpha$  protein levels can be determined by immunoprecipitations or immunohistochemistry using an antibody that specifically recognizes the protein product of SEQ ID Nos: 2, 4, or 100.

30           Agents that are identified as active in the drug screening assay are candidates to be tested for their capacity to block cell proliferation activity. These agents would be useful for treating a disorder involving aberrant growth of cells, especially colon cells, especially colorectal cancer.

A variety of assay formats will suffice and, in light of the present disclosure, those not expressly described herein will nevertheless be comprehended by one of ordinary skill in the art. For instance, the assay can be generated in many different formats, and include assays based on cell-free systems, e.g., purified proteins or cell lysates, as well as cell-based assays which utilize  
5 intact cells.

In many drug screening programs which test libraries of compounds and natural extracts, high throughput assays are desirable in order to maximize the number of compounds surveyed in a given period of time. Assays of the present invention which are performed in cell-free systems, such as may be derived with purified or semi-purified proteins or with lysates, or with proteins  
10 purified or semi-purified from serum, are often preferred as "primary" screens in that they can be generated to permit rapid development and relatively easy detection of an alteration in a molecular target which is mediated by a test compound. Moreover, the effects of cellular toxicity and/or bioavailability of the test compound can be generally ignored in the *in vitro* system, the assay instead being focused primarily on the effect of the drug on the molecular target as may be  
15 manifest in an alteration of binding affinity with other proteins or changes in enzymatic properties of the molecular target.

## EXAMPLES

The examples below are non-limiting and are merely representative of various aspects and features of the present invention.

### 20 Example 1: Generation of anti-Reg1 $\alpha$ antibodies

To generate antibodies to Reg1 $\alpha$ , the full-length open reading frame of Reg1 $\alpha$  (shown in either SEQ ID NO: 1 or 3) was directionally cloned into a mammalian expression vector, such as pcDNA3.1/V5-His (Invitrogen), which includes C-terminal epitope and purification tags. The insert sequence was verified by dideoxy sequencing (see, for example, Ausubel et al., Current  
25 Protocols in Molecular Biology, John Wiley and Sons). Recombinant fusion protein was produced in a transient expression system in mammalian cells (e.g. CHO cells). The recombinant protein was purified from the cell culture supernatants by immobilized metal affinity chromatography (IMAC) by utilizing the C terminal His-tag. The sequence of the Reg1 $\alpha$  protein used for the production of antibodies of the present invention is shown in either of SEQ  
30 ID Nos 2 or 4, all of which represent a functional Reg1 $\alpha$  protein, and which are encoded by SEQ ID Nos 1 or 3, respectively. The purified, recombinant Reg1 $\alpha$  protein was emulsified in

Freund's adjuvant and injected into rabbits. The animals were periodically boosted until they elicited a reasonable serum titer of specific antibody to Reg1 $\alpha$ . Methods for antibody production are well known to those of skill in the art and may be found, for example, in Harlow et al.

Antibodies: A laboratory manual, 1988, Cold Spring Harbor Laboratory. The polyclonal

- 5 antibodies, which recognized both native and denatured Reg1 $\alpha$ , were utilized to develop a microtiter-based ELISA assay. Methods of performing an ELISA assay are well known to those of skill in the art (see, for example, Asusbel et al., *supra*).

#### Example 2: Detection of Reg1 $\alpha$ in Colorectal cancer Patient Serum Samples

- The present invention relates to a method for the detection of colorectal cancer in an individual, which method includes the detection of Reg1 $\alpha$  polypeptides in a serum sample from an individual with colorectal cancer, wherein the detection of Reg1 $\alpha$  is indicative of the presence of colorectal cancer. Accordingly, Reg1 $\alpha$  expression was measured in serum samples obtained from patients having been diagnosed with colorectal cancer.

- All patients used in this study were diagnosed at their respective medical institutions by qualified physicians using conventional diagnostic means, including physical exam, blood analysis, imaging, and endoscopy. Once identified, patients provided informed consent through an IRB approved protocol. The severity of colorectal cancer in each patient was graded using the Dukes staging scheme. Serum samples were subsequently collected from each patient using methods known to those of skill in the art. Samples were subsequently assessed for the presence of Reg1 $\alpha$  by the ELISA assay described above. Figure 1 shows the levels of Reg1 $\alpha$  protein measured in the colorectal cancer patients compared to samples obtained from naïve patients and additional patients diagnosed with either inflammatory bowel disease (IBD) or cirrhosis of the liver. Figure 2 shows the levels of Reg1 $\alpha$  expression in the colorectal cancer patients of Figure 1, identified at each stage of colorectal cancer severity. As can be seen in Figures 1 and 2, Reg1 $\alpha$  expression is clearly elevated in serum samples obtained from patients diagnosed with colorectal cancer, and therefore may be used to detect the presence of colorectal cancer in a patient.

#### Example 3: Detection of Reg1 $\alpha$ Nucleic Acid Sequence in Colorectal cancer

- In one embodiment, the present invention provides for a method of detecting the presence of colorectal cancer in a patient by detecting the presence of nucleic acid molecules encoding Reg1 $\alpha$  in a serum sample obtained from a patient.



Serum may be obtained from a patient suspected of having colorectal cancer by methods described above and known to those of skill in the art. Nucleic acid molecules encoding Reg1 $\alpha$  may be detected, for example, by Northern analysis. Briefly, probes for detection of Reg1 $\alpha$  mRNA in a patient sample are derived by amplifying the Reg1 $\alpha$  coding sequence by RT-PCR according to techniques known in the art. The cDNA fragments generated in this manner are subsequently cloned into a PCRII vector using the TA cloning kit (Invitrogen). The identity of each fragment can be verified by sequencing in each direction from the T3 and T7 polymerase sites present in the cloning vector. The cDNA molecules produced in this manner are then used to produce <sup>32</sup>P-labeled Reg1 $\alpha$  cDNA probes using, for example, the Prime-It kit from Stratagene.

Subsequently, 5 to 10  $\mu$ g of total RNA isolated the serum of a patient suspected of having colorectal cancer is separated on an agarose/formaldehyde gel in 1X MOPS buffer. Methods of isolating RNA from a patient sample such as serum are well known in the art (see, for example, Ausubel et al., *supra*). Following staining with ethidium bromide and visualization under ultra violet light to determine the integrity of the RNA, the RNA is hydrolyzed by treatment with 0.05M NaOH/1.5M NaCl followed by incubation with 0.5M Tris-Cl (pH 7.4)/1.5M NaCl. The RNA is transferred to a commercially available nylon or nitrocellulose membrane (e.g. Hybond-N membrane, Amersham, Arlington Heights, IL) by methods well known in the art (Ausubel et al., *supra*, Sambrook et al., *supra*). Following transfer and UV cross linking, the membrane is hybridized with a <sup>32</sup>P-labeled Reg1 $\alpha$  cDNA probe in hybridization solution (e.g. in 50% formamide/2.5% Denhardt's/100-200mg denatured salmon sperm DNA/0.1% SDS/5X SSPE) overnight at 65°C. The hybridization conditions can be varied as necessary as described in Ausubel et al., *supra* and Sambrook et al., *supra*. Following hybridization, the membrane is washed at room temperature in 2X SSC/0.1% SDS, at 42°C in 1X SSC/0.1% SDS, at 65°C in 0.2X SSC/0.1% SDS, and exposed to film overnight with an intensifying screen at -80° C. The stringency of the wash buffers can also be varied depending on the amount of background signal (Ausubel et al., *supra*). The film is subsequently developed and the intensity bands corresponding to the radiolabeled probe hybridized to RNA are quantified using methods known to those of skill in the art, for example, by digitizing the film and analyzing the band intensity with a computer software program such as NIH Image (NIH, Bethesda, MD).

Alternatively, Reg1 $\alpha$  mRNA may be detected in a patient sample by real-time amplification using oligonucleotide primers capable of specifically hybridizing to the Reg1 $\alpha$  sequence. For example, real-time PCR and TaqMan® probes may be used to detect and quantitate the presence of Reg1 $\alpha$  mRNA in a patient sample. The technique of real-time PCR is

well known in the art (see, for example, U.S. Pat. Nos. 5,691,146; 5,779,977; 5,866,336; and 5,914,230). Methods of designing primers useful for the amplification of Reg1 $\alpha$  sequences are well known in the art (see, for example, Ausubel et al., *supra*)

5 cDNA samples, reverse transcribed from mRNA obtained from patient serum samples may be used to generate PCR products via an ABI 7700 sequence detection system (Applied Biosystems, Foster City, CA). A measurement may then be made of the level of expression of Reg1 $\alpha$  in the patient sample to determine if Reg1 $\alpha$  mRNA levels are elevated, thus, providing a means for the detection of colorectal cancer in the patient.

#### Example 4: Detection of Reg1 $\alpha$ in Other Patient Samples

10 In one embodiment of the present invention, colorectal cancer may be detected in a patient by detecting the expression of Reg1 $\alpha$  in a clinical patient sample, which is not a serum sample. For example, a circulating cell sample may be obtained from a patient by collecting a sample such as blood, stool, or other bodily fluid. The sample is then subsequently treated to lyse the cells present therein, for example by treating the sample with a suitable lysis buffer, such  
15 as a buffer containing 30 mM Tris-Cl, pH 7.4, 100 mM NaCl, 5 mM EDTA, 1% (w/v) SDS, and 100  $\mu$ g/ml proteinase K (for isolation of nucleic acid). The resulting sample is then analyzed for Reg1 $\alpha$  expression either by isolating total RNA from the sample, as described above, and in Ausubel et al., *supra*, or the sample may be separated on a polyacrylamide gel for analysis by Western blot, or may be utilized in an ELISA-based assay as described above in Example 2.

#### 20 Example 5. Detection of TIMP1 in patient serum samples

The present invention provides for the detection and monitoring of colorectal cancer in a patient by measuring the level of TIMP1 polypeptide in a patient sample, preferably in a plasma sample. TIMP1 expression was determined in 63 samples from patients diagnosed with colorectal cancer relative to the expression level of TIMP1 in 35 healthy individuals. The results  
25 demonstrate that TIMP1, in addition to one or more other colorectal cancer associated markers is overexpressed in colorectal cancer samples relative to normal samples, thus indicating that TIMP1 is a valuable marker for the detection of colorectal cancer in a patient (Figure 3).

To assess TIMP1 polypeptide expression levels, 63 pre-treatment plasma samples from patients with colorectal cancer, and 35 samples from healthy donors were tested in either  
30 commercially available ELISAs (Osteopontin), ADVIA Centaur Immunoassays (CEA and

Ferritin), or in-house developed ELISA (TIMP1). All patients used in this study were diagnosed at their respective medical institutions by qualified physicians using conventional diagnostic means, including physical exam, blood analysis, imaging, or endoscopy. Once identified, patients provided informed consent through an IRB approved protocol. The extent of colorectal cancer in each patient was determined using the Dukes' staging scheme. Serum and plasma samples were subsequently collected from each patient using methods known to those of skill in the art.

Specificity at appropriate cutoff values was determined for each marker (e.g., TIMP1, osteopontin, CEA, and ferritin) by evaluating the normal samples. For example, the 100% specificity cutoff for any given marker is equal to the marker value of the highest normal sample. Using these values as the cutoffs, the levels of each marker in the 63 cancer samples were compared to their own respective cutoff values. If the level in the cancer sample was higher than the determined cutoff value, the sample was deemed "positive" and is represented by a shaded box (Figure 3). This same process was repeated at 97% specificity (using the second highest normal; e.g., 34 of the 35 samples were equal to or below this value). The overall specificity level for the entire panel is calculated by multiplying the specificity of each marker in the panel (e.g.,  $97\% \times 97\% \times 97\% \times 97\% = 89\%$  specificity for the panel). The markers were arranged on the graphs shown in Figure 3, according to the frequency of their overexpression in the cancer samples (TIMP1 was overexpressed in the highest number of cancer patients and is therefore listed first). The marker adding the most to the sensitivity of TIMP1 is ranked second. For example, the 57% sensitivity/100% specificity graph shows that TIMP1 was elevated in 19 of the 63 colorectal cancer patient plasma samples, and is thus listed first on the graph. Evaluating the samples for osteopontin yielded seven additional positive patient samples, and osteopontin is thus listed second on the graph.

The sensitivity of the panel was determined by dividing the cumulative number of samples that were positive for at least one marker by the total number of cancer samples (63).

Other embodiments will be evident to those of skill in the art. It should be understood that the foregoing detailed description is provided for clarity only and is merely exemplary. The spirit and scope of the present invention are not limited to the above examples, but are encompassed by the following claims.

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<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<400> 45

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<211> 1650

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<213> Homo sapiens

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   248

	100		105		110
	Cys Cys Ser Gln Ser Glu Glu Gly Arg His Asn Cys Phe Leu Ala His				
	115		120		125
	Lys Lys Pro Thr Pro Ala Ser Ile Pro Leu Phe Gln Val Pro Glu Pro				
5	130		135		140
	Val Thr Ser Cys Glu Ala Tyr Glu Glu Asp Arg Glu Thr Phe Met Asn				
	145		150		155
	Lys Phe Ile Tyr Glu Ile Ala Arg Arg His Pro Phe Leu Tyr Ala Pro				
		165		170	175
10	Thr Ile Leu Leu Trp Ala Ala Arg Tyr Asp Lys Ile Ile Pro Ser Cys				
	180		185		190
	Cys Lys Ala Glu Asn Ala Val Glu Cys Phe Gln Thr Lys Ala Ala Thr				
	195		200		205
	Val Thr Lys Glu Leu Arg Glu Ser Ser Leu Leu Asn Gln His Ala Cys				
15	210		215		220
	Ala Val Met Lys Asn Phe Gly Thr Arg Thr Phe Gln Ala Ile Thr Val				
	225		230		235
	Thr Lys Leu Ser Gln Lys Phe Thr Lys Val Asn Phe Thr Glu Ile Gln				
		245		250	255
20	Lys Leu Val Leu Asp Val Ala His Val His Glu His Cys Cys Arg Gly				
	260		265		270
	Asp Val Leu Asp Cys Leu Gln Asp Gly Glu Lys Ile Met Ser Tyr Ile				
	275		280		285
	Cys Ser Gln Gln Asp Thr Leu Ser Asn Lys Ile Thr Glu Cys Cys Lys				
25	290		295		300
	Leu Thr Thr Leu Glu Arg Gly Gln Cys Ile Ile His Ala Glu Asn Asp				
	305		310		315
	Glu Lys Pro Glu Gly Leu Ser Pro Asn Leu Asn Arg Phe Leu Gly Asp				
		325		330	335

Arg Asp Phe Asn Gln Phe Ser Ser Gly Glu Lys Asn Ile Phe Leu Ala  
 340 345 350  
 Ser Phe Val His Glu Tyr Ser Arg Arg His Pro Gln Leu Ala Val Ser  
 355 360 365  
 5 Val Ile Leu Arg Val Ala Lys Gly Tyr Gln Glu Leu Leu Glu Lys Cys  
 370 375 380  
 Phe Gln Thr Glu Asn Pro Leu Glu Cys Gln Asp Lys Gly Glu Glu Glu  
 385 390 395 400  
 Leu Gln Lys Tyr Ile Gln Glu Ser Gln Ala Leu Ala Lys Arg Ser Cys  
 10 405 410 415  
 Gly Leu Phe Gln Lys Leu Gly Glu Tyr Tyr Leu Gln Asn Ala Phe Leu  
 420 425 430  
 Val Ala Tyr Thr Lys Lys Ala Pro Gln Leu Thr Ser Ser Glu Leu Met  
 435 440 445  
 15 Ala Ile Thr Arg Lys Met Ala Ala Thr Ala Ala Thr Cys Cys Gln Leu  
 450 455 460  
 Ser Glu Asp Lys Leu Leu Ala Cys Gly Glu Gly Ala Ala Asp Ile Ile  
 465 470 475 480  
 Ile Gly His Leu Cys Ile Arg His Glu Met Thr Pro Val Asn Pro Gly  
 20 485 490 495  
 Val Gly Gln Cys Cys Thr Ser Ser Tyr Ala Asn Arg Arg Pro Cys Phe  
 500 505 510  
 Ser Ser Leu Val Val Asp Glu Thr Tyr Val Pro Pro Ala Phe Ser Asp  
 515 520 525  
 25 Asp Lys Phe Ile Phe His Lys Asp Leu Cys Gln Ala Gln Gly Val Ala  
 530 535 540  
 Leu Gln Thr Met Lys Gln Glu Phe Leu Ile Asn Leu Val Lys Gln Lys  
 545 550 555 560  
 Pro Gln Ile Thr Glu Glu Gln Leu Glu Ala Val Ile Ala Asp Phe Ser  
 250

565                      570                      575  
 Gly Leu Leu Glu Lys Cys Cys Gln Gly Gln Glu Gln Glu Val Cys Phe  
                     580                      585                      590  
 Ala Glu Glu Gly Gln Lys Leu Ile Ser Lys Thr Arg Ala Ala Leu Gly  
 5                      595                      600                      605  
 Val

10 <210> 74  
     <211> 99  
     <212> PRT  
     <213> Homo sapiens

15 <400> 74  
 Met Thr Ser Lys Leu Ala Val Ala Leu Leu Ala Ala Phe Leu Ile Ser  
     1                      5                      10                      15  
 Ala Ala Leu Cys Glu Gly Ala Val Leu Pro Arg Ser Ala Lys Glu Leu  
                     20                      25                      30  
 20 Arg Cys Gln Cys Ile Lys Thr Tyr Ser Lys Pro Phe His Pro Lys Phe  
                     35                      40                      45  
 Ile Lys Glu Leu Arg Val Ile Glu Ser Gly Pro His Cys Ala Asn Thr  
                     50                      55                      60  
 Glu Ile Ile Val Lys Leu Ser Asp Gly Arg Glu Leu Cys Leu Asp Pro  
 25 65                      70                      75                      80  
 Lys Glu Asn Trp Val Gln Arg Val Val Glu Lys Phe Leu Lys Arg Ala  
                     85                      90                      95  
 Glu Asn Ser



<210> 75

<211> 300

5 <212> PRT

<213> Homo sapiens

<400> 75

Met Arg Ile Ala Val Ile Cys Phe Cys Leu Leu Gly Ile Thr Cys Ala  
10 1 5 10 15  
Ile Pro Val Lys Gln Ala Asp Ser Gly Ser Ser Glu Glu Lys Gln Leu  
20 25 30  
Tyr Asn Lys Tyr Pro Asp Ala Val Ala Thr Trp Leu Asn Pro Asp Pro  
35 40 45  
15 Ser Gln Lys Gln Asn Leu Leu Ala Pro Gln Thr Leu Pro Ser Lys Ser  
50 55 60  
Asn Glu Ser His Asp His Met Asp Asp Met Asp Asp Glu Asp Asp Asp  
65 70 75 80  
Asp His Val Asp Ser Gln Asp Ser Ile Asp Ser Asn Asp Ser Asp Asp  
20 85 90 95  
Val Asp Asp Thr Asp Asp Ser His Gln Ser Asp Glu Ser His His Ser  
100 105 110  
Asp Glu Ser Asp Glu Leu Val Thr Asp Phe Pro Thr Asp Leu Pro Ala  
115 120 125  
25 Thr Glu Val Phe Thr Pro Val Val Pro Thr Val Asp Thr Tyr Asp Gly  
130 135 140  
Arg Gly Asp Ser Val Val Tyr Gly Leu Arg Ser Lys Ser Lys Lys Phe  
145 150 155 160  
Arg Arg Pro Asp Ile Gln Tyr Pro Asp Ala Thr Asp Glu Asp Ile Thr

	165	170	175
	Ser His Met Glu Ser Glu Glu Leu Asn Gly Ala Tyr Lys Ala Ile Pro		
	180	185	190
	Val Ala Gln Asp Leu Asn Ala Pro Ser Asp Trp Asp Ser Arg Gly Lys		
5	195	200	205
	Asp Ser Tyr Glu Thr Ser Gln Leu Asp Asp Gln Ser Ala Glu Thr His		
	210	215	220
	Ser His Lys Gln Ser Arg Leu Tyr Lys Arg Lys Ala Asn Asp Glu Ser		
	225	230	235 240
10	Asn Glu His Ser Asp Val Ile Asp Ser Gln Glu Leu Ser Lys Val Ser		
	245	250	255
	Arg Glu Phe His Ser His Glu Phe His Ser His Glu Asp Met Leu Val		
	260	265	270
	Val Asp Pro Lys Ser Lys Glu Glu Asp Lys His Leu Lys Phe Arg Ile		
15	275	280	285
	Ser His Glu Leu Asp Ser Ala Ser Ser Glu Val Asn		
	290	295	300

20 <210> 76  
 <211> 871  
 <212> PRT  
 <213> Homo sapiens

25 <400> 76

Met Lys Tyr Ser Cys Cys Ala Leu Val Leu Ala Val Leu Gly Thr Glu
1 5 10 15
Leu Leu Gly Ser Leu Cys Ser Thr Val Arg Ser Pro Arg Phe Arg Gly
20 25 30
253

Arg Ile Gln Gln Glu Arg Lys Asn Ile Arg Pro Asn Ile Ile Leu Val  
 35 40 45  
 Leu Thr Asp Asp Gln Asp Val Glu Leu Gly Ser Leu Gln Val Met Asn  
 50 55 60  
 5 Lys Thr Arg Lys Ile Met Glu His Gly Gly Ala Thr Phe Ile Asn Ala  
 65 70 75 80  
 Phe Val Thr Thr Pro Met Cys Cys Pro Ser Arg Ser Ser Met Leu Thr  
 85 90 95  
 Gly Lys Tyr Val His Asn His Asn Val Tyr Thr Asn Asn Glu Asn Cys  
 10 100 105 110  
 Ser Ser Pro Ser Trp Gln Ala Met His Glu Pro Arg Thr Phe Ala Val  
 115 120 125  
 Tyr Leu Asn Asn Thr Gly Tyr Arg Thr Ala Phe Phe Gly Lys Tyr Leu  
 130 135 140  
 15 Asn Glu Tyr Asn Gly Ser Tyr Ile Pro Pro Gly Trp Arg Glu Trp Leu  
 145 150 155 160  
 Gly Leu Ile Lys Asn Ser Arg Phe Tyr Asn Tyr Thr Val Cys Arg Asn  
 165 170 175  
 Gly Ile Lys Glu Lys His Gly Phe Asp Tyr Ala Lys Asp Tyr Phe Thr  
 20 180 185 190  
 Asp Leu Ile Thr Asn Glu Ser Ile Asn Tyr Phe Lys Met Ser Lys Arg  
 195 200 205  
 Met Tyr Pro His Arg Pro Val Met Met Val Ile Ser His Ala Ala Pro  
 210 215 220  
 25 His Gly Pro Glu Asp Ser Ala Pro Gln Phe Ser Lys Leu Tyr Pro Asn  
 225 230 235 240  
 Ala Ser Gln His Ile Thr Pro Ser Tyr Asn Tyr Ala Pro Asn Met Asp  
 245 250 255  
 Lys His Trp Ile Met Gln Tyr Thr Gly Pro Met Leu Pro Ile His Met  
 254

	260	265	270
	Glu Phe Thr Asn Ile Leu Gln Arg Lys Arg Leu Gln Thr Leu Met Ser		
	275	280	285
	Val Asp Asp Ser Val Glu Arg Leu Tyr Asn Met Leu Val Glu Thr Gly		
5	290	295	300
	Glu Leu Glu Asn Thr Tyr Ile Ile Tyr Thr Ala Asp His Gly Tyr His		
	305	310	315 320
	Ile Gly Gln Phe Gly Leu Val Lys Gly Lys Ser Met Pro Tyr Asp Phe		
	325	330	335
10	Asp Ile Arg Val Pro Phe Phe Ile Arg Gly Pro Ser Val Glu Pro Gly		
	340	345	350
	Ser Ile Val Pro Gln Ile Val Leu Asn Ile Asp Leu Ala Pro Thr Ile		
	355	360	365
	Leu Asp Ile Ala Gly Leu Asp Thr Pro Pro Asp Val Asp Gly Lys Ser		
15	370	375	380
	Val Leu Lys Leu Leu Asp Pro Glu Lys Pro Gly Asn Arg Phe Arg Thr		
	385	390	395 400
	Asn Lys Lys Ala Lys Ile Trp Arg Asp Thr Phe Leu Val Glu Arg Gly		
	405	410	415
20	Lys Phe Leu Arg Lys Lys Glu Glu Ser Ser Lys Asn Ile Gln Gln Ser		
	420	425	430
	Asn His Leu Pro Lys Tyr Glu Arg Val Lys Glu Leu Cys Gln Gln Ala		
	435	440	445
	Arg Tyr Gln Thr Ala Cys Glu Gln Pro Gly Gln Lys Trp Gln Cys Ile		
25	450	455	460
	Glu Asp Thr Ser Gly Lys Leu Arg Ile His Lys Cys Lys Gly Pro Ser		
	465	470	475 480
	Asp Leu Leu Thr Val Arg Gln Ser Thr Arg Asn Leu Tyr Ala Arg Gly		
	485	490	495
	255		

Phe His Asp Lys Asp Lys Glu Cys Ser Cys Arg Glu Ser Gly Tyr Arg  
 500 505 510  
 Ala Ser Arg Ser Gln Arg Lys Ser Gln Arg Gln Phe Leu Arg Asn Gln  
 515 520 525  
 5 Gly Thr Pro Lys Tyr Lys Pro Arg Phe Val His Thr Arg Gln Thr Arg  
 530 535 540  
 Ser Leu Ser Val Glu Phe Glu Gly Glu Ile Tyr Asp Ile Asn Leu Glu  
 545 550 555 560  
 Glu Glu Glu Glu Leu Gln Val Leu Gln Pro Arg Asn Ile Ala Lys Arg  
 10 565 570 575  
 His Asp Glu Gly His Lys Gly Pro Arg Asp Leu Gln Ala Ser Ser Gly  
 580 585 590  
 Gly Asn Arg Gly Arg Met Leu Ala Asp Ser Ser Asn Ala Val Gly Pro  
 595 600 605  
 15 Pro Thr Thr Val Arg Val Thr His Lys Cys Phe Ile Leu Pro Asn Asp  
 610 615 620  
 Ser Ile His Cys Glu Arg Glu Leu Tyr Gln Ser Ala Arg Ala Trp Lys  
 625 630 635 640  
 Asp His Lys Ala Tyr Ile Asp Lys Glu Ile Glu Ala Leu Gln Asp Lys  
 20 645 650 655  
 Ile Lys Asn Leu Arg Glu Val Arg Gly His Leu Lys Arg Arg Lys Pro  
 660 665 670  
 Glu Glu Cys Ser Cys Ser Lys Gln Ser Tyr Tyr Asn Lys Glu Lys Gly  
 675 680 685  
 25 Val Lys Lys Gln Glu Lys Leu Lys Ser His Leu His Pro Phe Lys Glu  
 690 695 700  
 Ala Ala Gln Glu Val Asp Ser Lys Leu Gln Leu Phe Lys Glu Asn Asn  
 705 710 715 720  
 Arg Arg Arg Lys Lys Glu Arg Lys Glu Lys Arg Arg Gln Arg Lys Gly  
 256

	725	730	735
	Glu Glu Cys Ser Leu Pro Gly Leu Thr Cys Phe Thr His Asp Asn Asn		
	740	745	750
	His Trp Gln Thr Ala Pro Phe Trp Asn Leu Gly Ser Phe Cys Ala Cys		
5	755	760	765
	Thr Ser Ser Asn Asn Asn Thr Tyr Trp Cys Leu Arg Thr Val Asn Glu		
	770	775	780
	Thr His Asn Phe Leu Phe Cys Glu Phe Ala Thr Gly Phe Leu Glu Tyr		
	785	790	795 800
10	Phe Asp Met Asn Thr Asp Pro Tyr Gln Leu Thr Asn Thr Val His Thr		
	805	810	815
	Val Glu Arg Gly Ile Leu Asn Gln Leu His Val Gln Leu Met Glu Leu		
	820	825	830
	Arg Ser Cys Gln Gly Tyr Lys Gln Cys Asn Pro Arg Pro Lys Asn Leu		
15	835	840	845
	Asp Val Gly Asn Lys Asp Gly Gly Ser Tyr Asp Leu His Arg Gly Gln		
	850	855	860
	Leu Trp Asp Gly Trp Glu Gly		
	865	870	
20			

<210> 77

<211> 470

<212> PRT

25 <213> Homo sapiens

<400> 77

Met Lys Phe Leu Leu Ile Leu Leu Leu Gln Ala Thr Ala Ser Gly Ala

1

5

10

15

Leu Pro Leu Asn Ser Ser Thr Ser Leu Glu Lys Asn Asn Val Leu Phe  
 20 25 30  
 Gly Glu Arg Tyr Leu Glu Lys Phe Tyr Gly Leu Glu Ile Asn Lys Leu  
 35 40 45  
 5 Pro Val Thr Lys Met Lys Tyr Ser Gly Asn Leu Met Lys Glu Lys Ile  
 50 55 60  
 Gln Glu Met Gln His Phe Leu Gly Leu Lys Val Thr Gly Gln Leu Asp  
 65 70 75 80  
 Thr Ser Thr Leu Glu Met Met His Ala Pro Arg Cys Gly Val Pro Asp  
 10 85 90 95  
 Leu His His Phe Arg Glu Met Pro Gly Gly Pro Val Trp Arg Lys His  
 100 105 110  
 Tyr Ile Thr Tyr Arg Ile Asn Asn Tyr Thr Pro Asp Met Asn Arg Glu  
 115 120 125  
 15 Asp Val Asp Tyr Ala Ile Arg Lys Ala Phe Gln Val Trp Ser Asn Val  
 130 135 140  
 Thr Pro Leu Lys Phe Ser Lys Ile Asn Thr Gly Met Ala Asp Ile Leu  
 145 150 155 160  
 Val Val Phe Ala Arg Gly Ala His Gly Asp Phe His Ala Phe Asp Gly  
 165 170 175  
 20 Lys Gly Gly Ile Leu Ala His Ala Phe Gly Pro Gly Ser Gly Ile Gly  
 180 185 190  
 Gly Asp Ala His Phe Asp Glu Asp Glu Phe Trp Thr Thr His Ser Gly  
 195 200 205  
 25 Gly Thr Asn Leu Phe Leu Thr Ala Val His Glu Ile Gly His Ser Leu  
 210 215 220  
 Gly Leu Gly His Ser Ser Asp Pro Lys Ala Val Met Phe Pro Thr Tyr  
 225 230 235 240  
 Lys Tyr Val Asp Ile Asn Thr Phe Arg Leu Ser Ala Asp Asp Ile Arg  
 258

	245	250	255
	Gly Ile Gln Ser Leu Tyr Gly Asp Pro Lys Glu Asn Gln Arg Leu Pro		
	260	265	270
	Asn Pro Asp Asn Ser Glu Pro Ala Leu Cys Asp Pro Asn Leu Ser Phe		
5	275	280	285
	Asp Ala Val Thr Thr Val Gly Asn Lys Ile Phe Phe Phe Lys Asp Arg		
	290	295	300
	Phe Phe Trp Leu Lys Val Ser Glu Arg Pro Lys Thr Ser Val Asn Leu		
	305	310	315 320
10	Ile Ser Ser Leu Trp Pro Thr Leu Pro Ser Gly Ile Glu Ala Ala Tyr		
	325	330	335
	Glu Ile Glu Ala Arg Asn Gln Val Phe Leu Phe Lys Asp Asp Lys Tyr		
	340	345	350
	Trp Leu Ile Ser Asn Leu Arg Pro Glu Pro Asn Tyr Pro Lys Ser Ile		
15	355	360	365
	His Ser Phe Gly Phe Pro Asn Phe Val Lys Lys Ile Asp Ala Ala Val		
	370	375	380
	Phe Asn Pro Arg Phe Tyr Arg Thr Tyr Phe Phe Val Asp Asn Gln Tyr		
	385	390	395 400
20	Trp Arg Tyr Asp Glu Arg Arg Gln Met Met Asp Pro Gly Tyr Pro Lys		
	405	410	415
	Leu Ile Thr Lys Asn Phe Gln Gly Ile Gly Pro Lys Ile Asp Ala Val		
	420	425	430
	Phe Tyr Ser Lys Asn Lys Tyr Tyr Tyr Phe Phe Gln Gly Ser Asn Gln		
25	435	440	445
	Phe Glu Tyr Asp Phe Leu Leu Gln Arg Ile Thr Lys Thr Leu Lys Ser		
	450	455	460
	Asn Ser Trp Phe Gly Cys		
	465	470	



<210> 78

<211> 165

5 <212> PRT

<213> Homo sapiens

<400> 78

Met Ala Pro Asn Ala Ser Cys Leu Cys Val His Val Arg Ser Glu Glu  
10 1 5 10 15  
Trp Asp Leu Met Thr Phe Asp Ala Asn Pro Tyr Asp Ser Val Lys Lys  
20 25 30  
Ile Lys Glu His Val Arg Ser Lys Thr Lys Val Pro Val Gln Asp Gln  
35 40 45  
15 Val Leu Leu Leu Gly Ser Lys Ile Leu Lys Pro Arg Arg Ser Leu Ser  
50 55 60  
Ser Tyr Gly Ile Asp Lys Glu Lys Thr Ile His Leu Thr Leu Lys Val  
65 70 75 80  
Val Lys Pro Ser Asp Glu Glu Leu Pro Leu Phe Leu Val Glu Ser Gly  
20 85 90 95  
Asp Glu Ala Lys Arg His Leu Leu Gln Val Arg Arg Ser Ser Ser Val  
100 105 110  
Ala Gln Val Lys Ala Met Ile Glu Thr Lys Thr Gly Ile Ile Pro Glu  
115 120 125  
25 Thr Gln Ile Val Thr Cys Asn Gly Lys Arg Leu Glu Asp Gly Lys Met  
130 135 140  
Met Ala Asp Tyr Gly Ile Arg Lys Gly Asn Leu Leu Phe Leu Ala Ser  
145 150 155 160  
Tyr Cys Ile Gly Gly

&lt;210&gt; 79

5 &lt;211&gt; 1464

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 79

10 Met Phe Ser Phe Val Asp Leu Arg Leu Leu Leu Leu Leu Ala Ala Thr  
     1                  5                  10                  15  
 Ala Leu Leu Thr His Gly Gln Glu Glu Gly Gln Val Glu Gly Gln Asp  
                   20                  25                  30  
 Glu Asp Ile Pro Pro Ile Thr Cys Val Gln Asn Gly Leu Arg Tyr His  
 15          35                  40                  45  
 Asp Arg Asp Val Trp Lys Pro Glu Pro Cys Arg Ile Cys Val Cys Asp  
     50                  55                  60  
 Asn Gly Lys Val Leu Cys Asp Asp Val Ile Cys Asp Glu Thr Lys Asn  
     65                  70                  75                  80  
 20 Cys Pro Gly Ala Glu Val Pro Glu Gly Glu Cys Cys Pro Val Cys Pro  
                   85                  90                  95  
 Asp Gly Ser Glu Ser Pro Thr Asp Gln Glu Thr Thr Gly Val Glu Gly  
                   100                  105                  110  
 Pro Lys Gly Asp Thr Gly Pro Arg Gly Pro Arg Gly Pro Ala Gly Pro  
 25          115                  120                  125  
 Pro Gly Arg Asp Gly Ile Pro Gly Gln Pro Gly Leu Pro Gly Pro Pro  
     130                  135                  140  
 Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala  
     145                  150                  155                  160  
   261

Pro Gln Leu Ser Tyr Gly Tyr Asp Glu Lys Ser Thr Gly Gly Ile Ser  
 165 170 175  
 Val Pro Gly Pro Met Gly Pro Ser Gly Pro Arg Gly Leu Pro Gly Pro  
 180 185 190  
 5 Pro Gly Ala Pro Gly Pro Gln Gly Phe Gln Gly Pro Pro Gly Glu Pro  
 195 200 205  
 Gly Glu Pro Gly Ala Ser Gly Pro Met Gly Pro Arg Gly Pro Pro Gly  
 210 215 220  
 Pro Pro Gly Lys Asn Gly Asp Asp Gly Glu Ala Gly Lys Pro Gly Arg  
 10 225 230 235 240  
 Pro Gly Glu Arg Gly Pro Pro Gly Pro Gln Gly Ala Arg Gly Leu Pro  
 245 250 255  
 Gly Thr Ala Gly Leu Pro Gly Met Lys Gly His Arg Gly Phe Ser Gly  
 260 265 270  
 15 Leu Asp Gly Ala Lys Gly Asp Ala Gly Pro Ala Gly Pro Lys Gly Glu  
 275 280 285  
 Pro Gly Ser Pro Gly Glu Asn Gly Ala Pro Gly Gln Met Gly Pro Arg  
 290 295 300  
 Gly Leu Pro Gly Glu Arg Gly Arg Pro Gly Ala Pro Gly Pro Ala Gly  
 20 305 310 315 320  
 Ala Arg Gly Asn Asp Gly Ala Thr Gly Ala Ala Gly Pro Pro Gly Pro  
 325 330 335  
 Thr Gly Pro Ala Gly Pro Pro Gly Phe Pro Gly Ala Val Gly Ala Lys  
 340 345 350  
 25 Gly Glu Ala Gly Pro Gln Gly Pro Arg Gly Ser Glu Gly Pro Gln Gly  
 355 360 365  
 Val Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Ala Ala Gly Pro  
 370 375 380  
 Ala Gly Asn Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Ala Asn  
 262

	385		390		395		400
	Gly Ala Pro Gly Ile Ala Gly Ala Pro Gly Phe Pro Gly Ala Arg Gly						
		405		410		415	
	Pro Ser Gly Pro Gln Gly Pro Gly Gly Pro Pro Gly Pro Lys Gly Asn						
5		420		425		430	
	Ser Gly Glu Pro Gly Ala Pro Gly Ser Lys Gly Asp Thr Gly Ala Lys						
		435		440		445	
	Gly Glu Pro Gly Pro Val Gly Val Gln Gly Pro Pro Gly Pro Ala Gly						
	450		455		460		
10	Glu Glu Gly Lys Arg Gly Ala Arg Gly Glu Pro Gly Pro Thr Gly Leu						
	465		470		475		480
	Pro Gly Pro Pro Gly Glu Arg Gly Gly Pro Gly Ser Arg Gly Phe Pro						
		485		490		495	
	Gly Ala Asp Gly Val Ala Gly Pro Lys Gly Pro Ala Gly Glu Arg Gly						
15		500		505		510	
	Ser Pro Gly Pro Ala Gly Pro Lys Gly Ser Pro Gly Glu Ala Gly Arg						
		515		520		525	
	Pro Gly Glu Ala Gly Leu Pro Gly Ala Lys Gly Leu Thr Gly Ser Pro						
	530		535		540		
20	Gly Ser Pro Gly Pro Asp Gly Lys Thr Gly Pro Pro Gly Pro Ala Gly						
	545		550		555		560
	Gln Asp Gly Arg Pro Gly Pro Pro Gly Pro Pro Gly Ala Arg Gly Gln						
		565		570		575	
	Ala Gly Val Met Gly Phe Pro Gly Pro Lys Gly Ala Ala Gly Glu Pro						
25		580		585		590	
	Gly Lys Ala Gly Glu Arg Gly Val Pro Gly Pro Pro Gly Ala Val Gly						
		595		600		605	
	Pro Ala Gly Lys Asp Gly Glu Ala Gly Ala Gln Gly Pro Pro Gly Pro						
	610		615		620		

Ala Gly Pro Ala Gly Glu Arg Gly Glu Gln Gly Pro Ala Gly Ser Pro  
 625                      630                      635                      640  
 Gly Phe Gln Gly Leu Pro Gly Pro Ala Gly Pro Pro Gly Glu Ala Gly  
                          645                      650                      655  
 5 Lys Pro Gly Glu Gln Gly Val Pro Gly Asp Leu Gly Ala Pro Gly Pro  
                          660                      665                      670  
 Ser Gly Ala Arg Gly Glu Arg Gly Phe Pro Gly Glu Arg Gly Val Gln  
                          675                      680                      685  
 Gly Pro Pro Gly Pro Ala Gly Pro Arg Gly Ala Asn Gly Ala Pro Gly  
 10           690                      695                      700  
 Asn Asp Gly Ala Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly Ser  
 705                      710                      715                      720  
 Gln Gly Ala Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Ala Ala  
                          725                      730                      735  
 15 Gly Leu Pro Gly Pro Lys Gly Asp Arg Gly Asp Ala Gly Pro Lys Gly  
                          740                      745                      750  
 Ala Asp Gly Ser Pro Gly Lys Asp Gly Val Arg Gly Leu Thr Gly Pro  
                          755                      760                      765  
 Ile Gly Pro Pro Gly Pro Ala Gly Ala Pro Gly Asp Lys Gly Glu Ser  
 20           770                      775                      780  
 Gly Pro Ser Gly Pro Ala Gly Pro Thr Gly Ala Arg Gly Ala Pro Gly  
 785                      790                      795                      800  
 Asp Arg Gly Glu Pro Gly Pro Pro Gly Pro Ala Gly Phe Ala Gly Pro  
                          805                      810                      815  
 25 Pro Gly Ala Asp Gly Gln Pro Gly Ala Lys Gly Glu Pro Gly Asp Ala  
                          820                      825                      830  
 Gly Ala Lys Gly Asp Ala Gly Pro Pro Gly Pro Ala Gly Pro Ala Gly  
                          835                      840                      845  
 Pro Pro Gly Pro Ile Gly Asn Val Gly Ala Pro Gly Ala Lys Gly Ala  
                          264

	850	855	860
	Arg Gly Ser Ala Gly Pro Pro Gly Ala Thr Gly Phe Pro Gly Ala Ala		
	865	870	875 880
	Gly Arg Val Gly Pro Pro Gly Pro Ser Gly Asn Ala Gly Pro Pro Gly		
5	885	890	895
	Pro Pro Gly Pro Ala Gly Lys Glu Gly Gly Lys Gly Pro Arg Gly Glu		
	900	905	910
	Thr Gly Pro Ala Gly Arg Pro Gly Glu Val Gly Pro Pro Gly Pro Pro		
	915	920	925
10	Gly Pro Ala Gly Glu Lys Gly Ser Pro Gly Ala Asp Gly Pro Ala Gly		
	930	935	940
	Ala Pro Gly Thr Pro Gly Pro Gln Gly Ile Ala Gly Gln Arg Gly Val		
	945	950	955 960
	Val Gly Leu Pro Gly Gln Arg Gly Glu Arg Gly Phe Pro Gly Leu Pro		
15	965	970	975
	Gly Pro Ser Gly Glu Pro Gly Lys Gln Gly Pro Ser Gly Ala Ser Gly		
	980	985	990
	Glu Arg Gly Pro Pro Gly Pro Met Gly Pro Pro Gly Leu Ala Gly Pro		
	995	1000	1005
20	Pro Gly Glu Ser Gly Arg Glu Gly Ala Pro Ala Ala Glu Gly Ser Pro		
	1010	1015	1020
	Gly Arg Asp Gly Ser Pro Gly Ala Lys Gly Asp Arg Gly Glu Thr Gly		
	1025	1030	1035 1040
	Pro Ala Gly Pro Pro Gly Ala Pro Gly Ala Pro Gly Ala Pro Gly Pro		
25	1045	1050	1055
	Val Gly Pro Ala Gly Lys Ser Gly Asp Arg Gly Glu Thr Gly Pro Ala		
	1060	1065	1070
	Gly Pro Ala Gly Pro Val Gly Pro Val Gly Ala Arg Gly Pro Ala Gly		
	1075	1080	1085
		265	

Pro Gln Gly Pro Arg Gly Asp Lys Gly Glu Thr Gly Glu Gln Gly Asp  
 1090 1095 1100  
 Arg Gly Ile Lys Gly His Arg Gly Phe Ser Gly Leu Gln Gly Pro Pro  
 1105 1110 1115 1120  
 5 Gly Pro Pro Gly Ser Pro Gly Glu Gln Gly Pro Ser Gly Ala Ser Gly  
 1125 1130 1135  
 Pro Ala Gly Pro Arg Gly Pro Pro Gly Ser Ala Gly Ala Pro Gly Lys  
 1140 1145 1150  
 Asp Gly Leu Asn Gly Leu Pro Gly Pro Ile Gly Pro Pro Gly Pro Arg  
 10 1155 1160 1165  
 Gly Arg Thr Gly Asp Ala Gly Pro Val Gly Pro Pro Gly Pro Pro Gly  
 1170 1175 1180  
 Pro Pro Gly Pro Pro Gly Pro Pro Ser Ala Gly Phe Asp Phe Ser Phe  
 1185 1190 1195 1200  
 15 Leu Pro Gln Pro Pro Gln Glu Lys Ala His Asp Gly Gly Arg Tyr Tyr  
 1205 1210 1215  
 Arg Ala Asp Asp Ala Asn Val Val Arg Asp Arg Asp Leu Glu Val Asp  
 1220 1225 1230  
 Thr Thr Leu Lys Ser Leu Ser Gln Gln Ile Glu Asn Ile Arg Ser Pro  
 20 1235 1240 1245  
 Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Lys Met  
 1250 1255 1260  
 Cys His Ser Asp Trp Lys Ser Gly Glu Tyr Trp Ile Asp Pro Asn Gln  
 1265 1270 1275 1280  
 25 Gly Cys Asn Leu Asp Ala Ile Lys Val Phe Cys Asn Met Glu Thr Gly  
 1285 1290 1295  
 Glu Thr Cys Val Tyr Pro Thr Gln Pro Ser Val Ala Gln Lys Asn Trp  
 1300 1305 1310  
 Tyr Ile Ser Lys Asn Pro Lys Asp Lys Arg His Val Trp Phe Gly Glu  
 266

	1315	1320	1325
	Ser Met Thr Asp Gly Phe Gln Phe Glu Tyr Gly Gly Gln Gly Ser Asp		
	1330	1335	1340
	Pro Ala Asp Val Ala Ile Gln Leu Thr Phe Leu Arg Leu Met Ser Thr		
5	1345	1350	1355 1360
	Glu Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Val Ala Tyr		
	1365	1370	1375
	Met Asp Gln Gln Thr Gly Asn Leu Lys Lys Ala Leu Leu Leu Lys Gly		
	1380	1385	1390
10	Ser Asn Glu Ile Glu Ile Arg Ala Glu Gly Asn Ser Arg Phe Thr Tyr		
	1395	1400	1405
	Ser Val Thr Val Asp Gly Cys Thr Ser His Thr Gly Ala Trp Gly Lys		
	1410	1415	1420
	Thr Val Ile Glu Tyr Lys Thr Thr Lys Ser Ser Arg Leu Pro Ile Ile		
15	1425	1430	1435 1440
	Asp Val Ala Pro Leu Asp Val Gly Ala Pro Asp Gln Glu Phe Gly Phe		
	1445	1450	1455
	Asp Val Gly Pro Val Cys Phe Leu		
	1460		

20

<210> 80

<211> 338

<212> PRT

25 <213> Homo sapiens

<400> 80

Met Ser Leu Ser Ala Phe Thr Leu Phe Leu Ala Leu Ile Gly Gly Thr

1

5

10

15



Ser Gly Gln Tyr Tyr Asp Tyr Asp Phe Pro Leu Ser Ile Tyr Gly Gln  
 20 25 30  
 Ser Ser Pro Asn Cys Ala Pro Glu Cys Asn Cys Pro Glu Ser Tyr Pro  
 35 40 45  
 5 Ser Ala Met Tyr Cys Asp Glu Leu Lys Leu Lys Ser Val Pro Met Val  
 50 55 60  
 Pro Pro Gly Ile Lys Tyr Leu Tyr Leu Arg Asn Asn Gln Ile Asp His  
 65 70 75 80  
 Ile Asp Glu Lys Ala Phe Glu Asn Val Thr Asp Leu Gln Trp Leu Ile  
 10 85 90 95  
 Leu Asp His Asn Leu Leu Glu Asn Ser Lys Ile Lys Gly Arg Val Phe  
 100 105 110  
 Ser Lys Leu Lys Gln Leu Lys Lys Leu His Ile Asn His Asn Asn Leu  
 115 120 125  
 15 Thr Glu Ser Val Gly Pro Leu Pro Lys Ser Leu Glu Asp Leu Gln Leu  
 130 135 140  
 Thr His Asn Lys Ile Thr Lys Leu Gly Ser Phe Glu Gly Leu Val Asn  
 145 150 155 160  
 Leu Thr Phe Ile His Leu Gln His Asn Arg Leu Lys Glu Asp Ala Val  
 20 165 170 175  
 Ser Ala Ala Phe Lys Gly Leu Lys Ser Leu Glu Tyr Leu Asp Leu Ser  
 180 185 190  
 Phe Asn Gln Ile Ala Arg Leu Pro Ser Gly Leu Pro Val Ser Leu Leu  
 195 200 205  
 25 Thr Leu Tyr Leu Asp Asn Asn Lys Ile Ser Asn Ile Pro Asp Glu Tyr  
 210 215 220  
 Phe Lys Arg Phe Asn Ala Leu Gln Tyr Leu Arg Leu Ser His Asn Glu  
 225 230 235 240  
 Leu Ala Asp Ser Gly Ile Pro Gly Asn Ser Phe Asn Val Ser Ser Leu  
 268

245                      250                      255  
 Val Glu Leu Asp Leu Ser Tyr Asn Lys Leu Lys Asn Ile Pro Thr Val  
                     260                      265                      270  
 Asn Glu Asn Leu Glu Asn Tyr Tyr Leu Glu Val Asn Gln Leu Glu Lys  
 5                      275                      280                      285  
 Phe Asp Ile Lys Ser Phe Cys Lys Ile Leu Gly Pro Leu Ser Tyr Ser  
                     290                      295                      300  
 Lys Ile Lys His Leu Arg Leu Asp Gly Asn Arg Ile Ser Glu Thr Ser  
 305                      310                      315                      320  
 10 Leu Pro Pro Asp Met Tyr Glu Cys Leu Arg Val Ala Asn Glu Val Thr  
                     325                      330                      335  
 Leu Asn

15

<210> 81  
 <211> 589  
 <212> PRT  
 <213> Homo sapiens

20

<400> 81  
 Met Ser Val Ser Val His Glu Asn Arg Lys Ser Arg Ala Ser Ser Gly  
                     1                      5                      10                      15  
 Ser Ile Asn Ile Tyr Leu Phe His Lys Ser Ser Tyr Ala Asp Ser Val  
 25                      20                      25                      30  
 Leu Thr His Leu Asn Leu Leu Arg Gln Gln Arg Leu Phe Thr Asp Val  
                     35                      40                      45  
 Leu Leu His Ala Gly Asn Arg Thr Phe Pro Cys His Arg Ala Val Leu  
                     50                      55                      60  
 269

Ala Ala Cys Ser Arg Tyr Phe Glu Ala Met Phe Ser Gly Gly Leu Lys  
 65                      70                      75                      80  
 Glu Ser Gln Asp Ser Glu Val Asn Phe Asp Asn Ser Ile His Pro Glu  
                     85                      90                      95  
 5 Val Leu Glu Leu Leu Leu Asp Tyr Ala Tyr Ser Ser Arg Val Ile Ile  
                     100                      105                      110  
 Asn Glu Glu Asn Ala Glu Ser Leu Leu Glu Ala Gly Asp Met Leu Glu  
                     115                      120                      125  
 Phe Gln Asp Ile Arg Asp Ala Cys Ala Glu Phe Leu Glu Lys Asn Leu  
 10            130                      135                      140  
 His Pro Thr Asn Cys Leu Gly Met Leu Leu Leu Ser Asp Ala His Gln  
 145                      150                      155                      160  
 Cys Thr Lys Leu Tyr Glu Leu Ser Trp Arg Met Cys Leu Ser Asn Phe  
                     165                      170                      175  
 15 Gln Thr Ile Arg Lys Asn Glu Asp Phe Leu Gln Leu Pro Gln Asp Met  
                     180                      185                      190  
 Val Val Gln Leu Leu Ser Ser Glu Glu Leu Glu Thr Glu Asp Glu Arg  
                     195                      200                      205  
 Leu Val Tyr Glu Ser Ala Ile Asn Trp Ile Ser Tyr Asp Leu Lys Lys  
 20            210                      215                      220  
 Arg Tyr Cys Tyr Leu Pro Glu Leu Leu Gln Thr Val Arg Leu Ala Leu  
 225                      230                      235                      240  
 Leu Pro Ala Ile Tyr Leu Met Glu Asn Val Ala Met Glu Glu Leu Ile  
                     245                      250                      255  
 25 Thr Lys Gln Arg Lys Ser Lys Glu Ile Val Glu Glu Ala Ile Arg Cys  
                     260                      265                      270  
 Lys Leu Lys Ile Leu Gln Asn Asp Gly Val Val Thr Ser Leu Cys Ala  
                     275                      280                      285  
 Arg Pro Arg Lys Thr Gly His Ala Leu Phe Leu Leu Gly Gly Gln Thr  
                     270

	290	295	300	
	Phe Met Cys Asp Lys Leu Tyr Leu Val Asp Gln Lys Ala Lys Glu Ile			
	305	310	315	320
	Ile Pro Lys Ala Asp Ile Pro Ser Pro Arg Lys Glu Phe Ser Ala Cys			
5	325	330	335	
	Ala Ile Gly Cys Lys Val Tyr Ile Thr Gly Gly Arg Gly Ser Glu Asn			
	340	345	350	
	Gly Val Ser Lys Asp Val Trp Val Tyr Asp Thr Leu His Glu Glu Trp			
	355	360	365	
10	Ser Lys Ala Ala Pro Met Leu Val Ala Arg Phe Gly His Gly Ser Ala			
	370	375	380	
	Glu Leu Lys His Cys Leu Tyr Val Val Gly Gly His Thr Ala Ala Thr			
	385	390	395	400
	Gly Cys Leu Pro Ala Ser Pro Ser Val Ser Leu Lys Gln Val Glu His			
15	405	410	415	
	Tyr Asp Pro Thr Ile Asn Lys Trp Thr Met Val Ala Pro Leu Arg Glu			
	420	425	430	
	Gly Val Ser Asn Ala Ala Val Val Ser Ala Lys Leu Lys Leu Phe Ala			
	435	440	445	
20	Phe Gly Gly Thr Ser Val Ser His Asp Lys Leu Pro Lys Val Gln Cys			
	450	455	460	
	Tyr Asp Gln Cys Glu Asn Arg Trp Thr Val Pro Ala Thr Cys Pro Gln			
	465	470	475	480
	Pro Trp Arg Tyr Thr Ala Ala Ala Val Leu Gly Asn Gln Ile Phe Ile			
25	485	490	495	
	Met Gly Gly Asp Thr Glu Phe Ser Ala Cys Ser Ala Tyr Lys Phe Asn			
	500	505	510	
	Ser Glu Thr Tyr Gln Trp Thr Lys Val Gly Asp Val Thr Ala Lys Arg			
	515	520	525	

Met Ser Cys His Ala Val Ala Ser Gly Asn Lys Leu Tyr Val Val Gly

530

535

540

Gly Tyr Phe Gly Ile Gln Arg Cys Lys Thr Leu Asp Cys Tyr Asp Pro

545

550

555

560

5 Thr Leu Asp Val Trp Asn Ser Ile Thr Thr Val Pro Tyr Ser Leu Ile

565

570

575

Pro Thr Ala Phe Val Ser Thr Trp Lys His Leu Pro Ser

580

585

10

<210> 82

<211> 193

<212> PRT

<213> Homo sapiens

15

<400> 82

Met Ile Arg Cys Gly Leu Ala Cys Glu Arg Cys Arg Trp Ile Leu Pro

1

5

10

15

Leu Leu Leu Leu Ser Ala Ile Ala Phe Asp Ile Ile Ala Leu Ala Gly

20

20

25

30

Arg Gly Trp Leu Gln Ser Ser Asp His Gly Gln Thr Ser Ser Leu Trp

35

40

45

Trp Lys Cys Ser Gln Glu Gly Gly Gly Ser Gly Ser Tyr Glu Glu Gly

50

55

60

25 Cys Gln Ser Leu Met Glu Tyr Ala Trp Gly Arg Ala Ala Ala Ala Met

65

70

75

80

Leu Phe Cys Gly Phe Ile Ile Leu Val Ile Cys Phe Ile Leu Ser Phe

85

90

95

Phe Ala Leu Cys Gly Pro Gln Met Leu Val Phe Leu Arg Val Ile Gly

272

100 105 110  
 Gly Leu Leu Ala Leu Ala Ala Val Phe Gln Ile Ile Ser Leu Val Ile  
 115 120 125  
 Tyr Pro Val Lys Tyr Thr Gln Thr Phe Thr Leu His Ala Asn Pro Ala  
 5 130 135 140  
 Val Thr Tyr Ile Tyr Asn Trp Ala Tyr Gly Phe Gly Trp Ala Ala Thr  
 145 150 155 160  
 Ile Ile Leu Ile Gly Cys Ala Phe Phe Phe Cys Cys Leu Leu Asn Tyr  
 165 170 175  
 10 Glu Asp Asp Leu Leu Gly Asn Ala Lys Pro Arg Tyr Phe Tyr Thr Ser  
 180 185 190  
 Ala

15

<210> 83  
 <211> 423  
 <212> PRT  
 <213> Homo sapiens

20

<400> 83  
 Met Arg Ser Ser Gly Ala Asp Ala Gly Arg Cys Leu Val Thr Ala Arg  
 1 5 10 15  
 Ala Pro Gly Ser Val Pro Ala Ser Arg Glu Gly Ser Ala Gly Ser Arg  
 25 20 25 30  
 Gly Pro Gly Ala Arg Phe Pro Ala Arg Val Ser Ala Arg Gly Ser Ala  
 35 40 45  
 Pro Gly Pro Gly Leu Gly Gly Ala Gly Ala Leu Asp Pro Pro Ala Val  
 50 55 60

Val Ala Glu Ser Val Ser Ser Leu Thr Ile Ala Asp Ala Phe Ile Ala  
65                      70                      75                      80  
Ala Gly Glu Ser Ser Ala Pro Thr Pro Pro Arg Pro Ala Leu Pro Arg  
                    85                      90                      95  
5 Arg Phe Ile Cys Ser Phe Pro Asp Cys Ser Ala Asn Tyr Ser Lys Ala  
                    100                      105                      110  
Trp Lys Leu Asp Ala His Leu Cys Lys His Thr Gly Glu Arg Pro Phe  
                    115                      120                      125  
Val Cys Asp Tyr Glu Gly Cys Gly Lys Ala Phe Ile Arg Asp Tyr His  
10            130                      135                      140  
Leu Ser Arg His Ile Leu Thr His Thr Gly Glu Lys Pro Phe Val Cys  
145                      150                      155                      160  
Ala Ala Asn Gly Cys Asp Gln Lys Phe Asn Thr Lys Ser Asn Leu Lys  
                    165                      170                      175  
15 Lys His Phe Glu Arg Lys His Glu Asn Gln Gln Lys Gln Tyr Ile Cys  
                    180                      185                      190  
Ser Phe Glu Asp Cys Lys Lys Thr Phe Lys Lys His Gln Gln Leu Lys  
                    195                      200                      205  
Ile His Gln Cys Gln Asn Thr Asn Glu Pro Leu Phe Lys Cys Thr Gln  
20            210                      215                      220  
Glu Gly Cys Gly Lys His Phe Ala Ser Pro Ser Lys Leu Lys Arg His  
225                      230                      235                      240  
Ala Lys Ala His Glu Gly Tyr Val Cys Gln Lys Gly Cys Ser Phe Val  
                    245                      250                      255  
25 Ala Lys Thr Trp Thr Glu Leu Leu Lys His Val Arg Glu Thr His Lys  
                    260                      265                      270  
Glu Glu Ile Leu Cys Glu Val Cys Arg Lys Thr Phe Lys Arg Lys Asp  
                    275                      280                      285  
Tyr Leu Lys Gln His Met Lys Thr His Ala Pro Glu Arg Asp Val Cys  
274

	290	295	300	
	Arg Cys Pro Arg Glu Gly Cys Gly Arg Thr Tyr Thr Thr Val Phe Asn			
	305	310	315	320
	Leu Gln Ser His Ile Leu Ser Phe His Glu Glu Ser Arg Pro Phe Val			
5	325	330	335	
	Cys Glu His Ala Gly Cys Gly Lys Thr Phe Ala Met Lys Gln Ser Leu			
	340	345	350	
	Thr Arg His Ala Val Val His Asp Pro Asp Lys Lys Lys Met Lys Leu			
	355	360	365	
10	Lys Val Lys Lys Ser Arg Glu Lys Arg Glu Phe Gly Leu Ser Ser Gln			
	370	375	380	
	Trp Ile Tyr Pro Pro Lys Arg Lys Gln Gly Gln Gly Leu Ser Leu Cys			
	385	390	395	400
	Gln Asn Gly Glu Ser Pro Asn Cys Val Glu Asp Lys Met Leu Ser Thr			
15	405	410	415	
	Val Ala Val Leu Thr Leu Gly			
	420			

20 <210> 84  
 <211> 339  
 <212> PRT  
 <213> Homo sapiens

25 <400> 84

Met Trp Gln Leu Trp Ala Ser Leu Cys Cys Leu Leu Val Leu Ala Asn
1                      5                      10                      15
Ala Arg Ser Arg Pro Ser Phe His Pro Leu Ser Asp Glu Leu Val Asn
20                      25                      30
275



Tyr Val Asn Lys Arg Asn Thr Thr Trp Gln Ala Gly His Asn Phe Tyr  
 35 40 45  
 Asn Val Asp Met Ser Tyr Leu Lys Arg Leu Cys Gly Thr Phe Leu Gly  
 50 55 60  
 5 Gly Pro Lys Pro Pro Gln Arg Val Met Phe Thr Glu Asp Leu Lys Leu  
 65 70 75 80  
 Pro Ala Ser Phe Asp Ala Arg Glu Gln Trp Pro Gln Cys Pro Thr Ile  
 85 90 95  
 Lys Glu Ile Arg Asp Gln Gly Ser Cys Gly Ser Cys Trp Ala Phe Gly  
 10 100 105 110  
 Ala Val Glu Ala Ile Ser Asp Arg Ile Cys Ile His Thr Asn Ala His  
 115 120 125  
 Val Ser Val Glu Val Ser Ala Glu Asp Leu Leu Thr Cys Cys Gly Ser  
 130 135 140  
 15 Met Cys Gly Asp Gly Cys Asn Gly Gly Tyr Pro Ala Glu Ala Trp Asn  
 145 150 155 160  
 Phe Trp Thr Arg Lys Gly Leu Val Ser Gly Gly Leu Tyr Glu Ser His  
 165 170 175  
 Val Gly Cys Arg Pro Tyr Ser Ile Pro Pro Cys Glu His His Val Asn  
 20 180 185 190  
 Gly Ser Arg Pro Pro Cys Thr Gly Glu Gly Asp Thr Pro Lys Cys Ser  
 195 200 205  
 Lys Ile Cys Glu Pro Gly Tyr Ser Pro Thr Tyr Lys Gln Asp Lys His  
 210 215 220  
 25 Tyr Gly Tyr Asn Ser Tyr Ser Val Ser Asn Ser Glu Lys Asp Ile Met  
 225 230 235 240  
 Ala Glu Ile Tyr Lys Asn Gly Pro Val Glu Gly Ala Phe Ser Val Tyr  
 245 250 255  
 Ser Asp Phe Leu Leu Tyr Lys Ser Gly Val Tyr Gln His Val Thr Gly  
 276



Ser Ser Tyr Tyr Lys Gly Gly Phe Glu Gln Lys Met Ser Arg Arg Glu  
                     85                    90                    95  
 Ala Gly Leu Ile Leu Gly Val Ser Pro Ser Ala Gly Lys Ala Lys Ile  
                     100                    105                    110  
 5 Arg Thr Ala His Arg Arg Val Met Ile Leu Asn His Pro Asp Lys Gly  
                     115                    120                    125  
 Gly Ser Pro Tyr Val Ala Ala Lys Ile Asn Glu Ala Lys Asp Leu Leu  
                     130                    135                    140  
 Glu Thr Thr Thr Lys His  
 10 145                    150

<210> 86

<211> 1212

15 <212> PRT

<213> Homo sapiens

<400> 86

Met Glu Pro Arg Pro Thr Ala Pro Ser Ser Gly Ala Pro Gly Leu Ala  
 20 1                    5                    10                    15  
 Gly Val Gly Glu Thr Pro Ser Ala Ala Ala Leu Ala Ala Ala Arg Val  
                     20                    25                    30  
 Glu Leu Pro Gly Thr Ala Val Pro Ser Val Pro Glu Asp Ala Ala Pro  
                     35                    40                    45  
 25 Ala Ser Arg Asp Gly Gly Gly Val Arg Asp Glu Gly Pro Ala Ala Ala  
                     50                    55                    60  
 Gly Asp Gly Leu Gly Arg Pro Leu Gly Pro Thr Pro Ser Gln Ser Arg  
                     65                    70                    75                    80  
 Phe Gln Val Asp Leu Val Ser Glu Asn Ala Gly Arg Ala Ala Ala Ala  
                                     278

	85	90	95
	Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Gly Ala Gly Ala Gly		
	100	105	110
	Ala Lys Gln Thr Pro Ala Asp Gly Glu Ala Ser Gly Glu Ser Glu Pro		
5	115	120	125
	Ala Lys Gly Ser Glu Glu Ala Lys Gly Arg Phe Arg Val Asn Phe Val		
	130	135	140
	Asp Pro Ala Ala Ser Ser Ser Ala Glu Asp Ser Leu Ser Asp Ala Ala		
	145	150	155
			160
10	Gly Val Gly Val Asp Gly Pro Asn Val Ser Phe Gln Asn Gly Gly Asp		
	165	170	175
	Thr Val Leu Ser Glu Gly Ser Ser Leu His Ser Gly Gly Gly Gly Gly		
	180	185	190
	Ser Gly His His Gln His Tyr Tyr Tyr Asp Thr His Thr Asn Thr Tyr		
15	195	200	205
	Tyr Leu Arg Thr Phe Gly His Asn Thr Met Asp Ala Val Pro Arg Ile		
	210	215	220
	Asp His Tyr Arg His Thr Ala Ala Gln Leu Gly Glu Lys Leu Leu Arg		
	225	230	235
			240
20	Pro Ser Leu Ala Glu Leu His Asp Glu Leu Glu Lys Glu Pro Phe Glu		
	245	250	255
	Asp Gly Phe Ala Asn Gly Glu Glu Ser Thr Pro Thr Arg Asp Ala Val		
	260	265	270
	Val Thr Tyr Thr Ala Glu Ser Lys Gly Val Val Lys Phe Gly Trp Ile		
25	275	280	285
	Lys Gly Val Leu Val Arg Cys Met Leu Asn Ile Trp Gly Val Met Leu		
	290	295	300
	Phe Ile Arg Leu Ser Trp Ile Val Gly Gln Ala Gly Ile Gly Leu Ser		
305	310	315	320
		279	

Val Leu Val Ile Met Met Ala Thr Val Val Thr Thr Ile Thr Gly Leu  
 325 330 335  
 Ser Thr Ser Ala Ile Ala Thr Asn Gly Phe Val Arg Gly Gly Gly Ala  
 340 345 350  
 5 Tyr Tyr Leu Ile Ser Arg Ser Leu Gly Pro Glu Phe Gly Gly Ala Ile  
 355 360 365  
 Gly Leu Ile Phe Ala Phe Ala Asn Ala Val Ala Val Ala Met Tyr Val  
 370 375 380  
 Val Gly Phe Ala Glu Thr Val Val Glu Leu Leu Lys Glu His Ser Ile  
 10 385 390 395 400  
 Leu Met Ile Asp Glu Ile Asn Asp Ile Arg Ile Ile Gly Ala Ile Thr  
 405 410 415  
 Val Val Ile Leu Leu Gly Ile Ser Val Ala Gly Met Glu Trp Glu Ala  
 420 425 430  
 15 Lys Ala Gln Ile Val Leu Leu Val Ile Leu Leu Leu Ala Ile Gly Asp  
 435 440 445  
 Phe Val Ile Gly Thr Phe Ile Pro Leu Glu Ser Lys Lys Pro Lys Gly  
 450 455 460  
 Phe Phe Gly Tyr Lys Ser Glu Ile Phe Asn Glu Asn Phe Gly Pro Asp  
 20 465 470 475 480  
 Phe Arg Glu Glu Glu Thr Phe Phe Ser Val Phe Ala Ile Phe Phe Pro  
 485 490 495  
 Ala Ala Thr Gly Ile Leu Ala Gly Ala Asn Ile Ser Gly Asp Leu Ala  
 500 505 510  
 25 Asp Pro Gln Ser Ala Ile Pro Lys Gly Thr Leu Leu Ala Ile Leu Ile  
 515 520 525  
 Thr Thr Leu Val Tyr Val Gly Ile Ala Val Ser Val Gly Ser Cys Val  
 530 535 540  
 Val Arg Asp Ala Thr Gly Asn Val Asn Asp Thr Ile Val Thr Glu Leu  
 280

	545	550	555	560
	Thr Asn Cys Thr Ser Ala Ala Cys Lys Leu Asn Phe Asp Phe Ser Ser			
	565	570	575	
	Cys Glu Ser Ser Pro Cys Ser Tyr Gly Leu Met Asn Asn Phe Gln Val			
5	580	585	590	
	Met Ser Met Val Ser Gly Phe Thr Pro Leu Ile Ser Ala Gly Ile Phe			
	595	600	605	
	Ser Ala Thr Leu Ser Ser Ala Leu Ala Ser Leu Val Ser Ala Pro Lys			
	610	615	620	
10	Ile Phe Gln Ala Leu Cys Lys Asp Asn Ile Tyr Pro Ala Phe Gln Met			
	625	630	635	640
	Phe Ala Lys Gly Tyr Gly Lys Asn Asn Glu Pro Leu Arg Gly Tyr Ile			
	645	650	655	
	Leu Thr Phe Leu Ile Ala Leu Gly Phe Ile Leu Ile Ala Glu Leu Asn			
15	660	665	670	
	Val Ile Ala Pro Ile Ile Ser Asn Phe Phe Leu Ala Ser Tyr Ala Leu			
	675	680	685	
	Ile Asn Phe Ser Val Phe His Ala Ser Leu Ala Lys Ser Pro Gly Trp			
	690	695	700	
20	Arg Pro Ala Phe Lys Tyr Tyr Asn Met Trp Ile Ser Leu Leu Gly Ala			
	705	710	715	720
	Ile Leu Cys Cys Ile Val Met Phe Val Ile Asn Trp Trp Ala Ala Leu			
	725	730	735	
	Leu Thr Tyr Val Ile Val Leu Gly Leu Tyr Ile Tyr Val Thr Tyr Lys			
25	740	745	750	
	Lys Pro Asp Val Asn Trp Gly Ser Ser Thr Gln Ala Leu Thr Tyr Leu			
	755	760	765	
	Asn Ala Leu Gln His Ser Ile Arg Leu Ser Gly Val Glu Asp His Val			
	770	775	780	

Lys Asn Phe Arg Pro Gln Cys Leu Val Met Thr Gly Ala Pro Asn Ser  
 785                      790                      795                      800  
 Arg Pro Ala Leu Leu His Leu Val His Asp Phe Thr Lys Asn Val Gly  
                          805                      810                      815  
 5 Leu Met Ile Cys Gly His Val His Met Gly Pro Arg Arg Gln Ala Met  
                          820                      825                      830  
 Lys Glu Met Ser Ile Asp Gln Ala Lys Tyr Gln Arg Trp Leu Ile Lys  
                          835                      840                      845  
 Asn Lys Met Lys Ala Phe Tyr Ala Pro Val His Ala Asp Asp Leu Arg  
 10                      850                      855                      860  
 Glu Gly Ala Gln Tyr Leu Met Gln Ala Ala Gly Leu Gly Arg Met Lys  
                          865                      870                      875                      880  
 Pro Asn Thr Leu Val Leu Gly Phe Lys Lys Asp Trp Leu Gln Ala Asp  
                          885                      890                      895  
 15 Met Arg Asp Val Asp Met Tyr Ile Asn Leu Phe His Asp Ala Phe Asp  
                          900                      905                      910  
 Ile Gln Tyr Gly Val Val Val Ile Arg Leu Lys Glu Gly Leu Asp Ile  
                          915                      920                      925  
 Ser His Leu Gln Gly Gln Glu Glu Leu Leu Ser Ser Gln Glu Lys Ser  
 20                      930                      935                      940  
 Pro Gly Thr Lys Asp Val Val Val Ser Val Glu Tyr Ser Lys Lys Ser  
                          945                      950                      955                      960  
 Asp Leu Asp Thr Ser Lys Pro Leu Ser Glu Lys Pro Ile Thr His Lys  
                          965                      970                      975  
 25 Val Glu Glu Glu Asp Gly Lys Thr Ala Thr Gln Pro Leu Leu Lys Lys  
                          980                      985                      990  
 Glu Ser Lys Gly Pro Ile Val Pro Leu Asn Val Ala Asp Gln Lys Leu  
                          995                      1000                      1005  
 Leu Glu Ala Ser Thr Gln Phe Gln Lys Lys Gln Gly Lys Asn Thr Ile  
 282

	1010	1015	1020	
	Asp Val Trp Trp Leu Phe Asp Asp Gly Gly Leu Thr Leu Leu Ile Pro			
	1025	1030	1035	1040
	Tyr Leu Leu Thr Thr Lys Lys Lys Trp Lys Asp Cys Lys Ile Arg Val			
5	1045	1050	1055	
	Phe Ile Gly Gly Lys Ile Asn Arg Ile Asp His Asp Arg Arg Ala Met			
	1060	1065	1070	
	Ala Thr Leu Leu Ser Lys Phe Arg Ile Asp Phe Ser Asp Ile Met Val			
	1075	1080	1085	
10	Leu Gly Asp Ile Asn Thr Lys Pro Lys Lys Glu Asn Ile Ile Ala Phe			
	1090	1095	1100	
	Glu Glu Ile Ile Glu Pro Tyr Arg Leu His Glu Asp Asp Lys Glu Gln			
	1105	1110	1115	1120
	Asp Ile Ala Asp Lys Met Lys Glu Asp Glu Pro Trp Arg Ile Thr Asp			
15	1125	1130	1135	
	Asn Glu Leu Glu Leu Tyr Lys Thr Lys Thr Tyr Arg Gln Ile Arg Leu			
	1140	1145	1150	
	Asn Glu Leu Leu Lys Glu His Ser Ser Thr Ala Asn Ile Ile Val Met			
	1155	1160	1165	
20	Ser Leu Pro Val Ala Arg Lys Gly Ala Val Ser Ser Ala Leu Tyr Met			
	1170	1175	1180	
	Ala Trp Leu Glu Ala Leu Ser Lys Asp Leu Pro Pro Ile Leu Leu Val			
	1185	1190	1195	1200
	Arg Gly Asn His Gln Ser Val Leu Thr Phe Tyr Ser			
25	1205	1210		

<210> 87

<211> 230



<212> PRT

<213> Homo sapiens

<400> 87

5 Met Asn Glu Met Tyr Leu Arg Cys Asp His Glu Asn Gln Tyr Ala Gln  
1 5 10 15  
Trp Met Ala Ala Cys Met Leu Ala Ser Lys Gly Lys Thr Met Ala Asp  
20 25 30  
Ser Ser Tyr Gln Pro Glu Val Leu Asn Ile Leu Ser Phe Leu Arg Met  
10 35 40 45  
Lys Asn Arg Asn Ser Ala Ser Gln Val Ala Ser Ser Leu Glu Asn Met  
50 55 60  
Asp Met Asn Pro Glu Cys Phe Val Ser Pro Arg Cys Ala Lys Arg His  
65 70 75 80  
15 Lys Ser Lys Gln Leu Ala Ala Arg Ile Leu Glu Ala His Gln Asn Val  
85 90 95  
Ala Gln Met Pro Leu Val Glu Ala Lys Leu Arg Phe Ile Gln Ala Trp  
100 105 110  
Gln Ser Leu Pro Glu Phe Gly Leu Thr Tyr Tyr Leu Val Arg Phe Lys  
20 115 120 125  
Gly Ser Lys Lys Asp Asp Ile Leu Gly Val Ser Tyr Asn Arg Leu Ile  
130 135 140  
Lys Ile Asp Ala Ala Thr Gly Ile Pro Val Thr Thr Trp Arg Phe Thr  
145 150 155 160  
25 Asn Ile Lys Gln Trp Asn Val Asn Trp Glu Thr Arg Gln Val Val Ile  
165 170 175  
Glu Phe Asp Gln Asn Val Phe Thr Ala Phe Thr Cys Leu Ser Ala Asp  
180 185 190  
Cys Lys Ile Val His Glu Tyr Ile Gly Gly Tyr Ile Phe Leu Ser Thr  
284

	195	200	205
	Arg Ser Lys Asp Gln Asn Glu Thr Leu Asp Glu Asp Leu Phe His Lys		
	210	215	220
	Leu Thr Gly Gly Gln Asp		
5	225	230	
	<210> 88		
	<211> 383		
10	<212> PRT		
	<213> Homo sapiens		
	<400> 88		
	Met Glu Ala Leu Gly Lys Leu Lys Gln Phe Asp Ala Tyr Pro Lys Thr		
15	1	5	10 15
	Leu Glu Asp Phe Arg Val Lys Thr Cys Gly Gly Ala Thr Val Thr Ile		
	20	25	30
	Val Ser Gly Leu Leu Met Leu Leu Leu Phe Leu Ser Glu Leu Gln Tyr		
	35	40	45
20	Tyr Leu Thr Thr Glu Val His Pro Glu Leu Tyr Val Asp Lys Ser Arg		
	50	55	60
	Gly Asp Lys Leu Lys Ile Asn Ile Asp Val Leu Phe Pro His Met Pro		
	65	70	75 80
	Cys Ala Tyr Leu Ser Ile Asp Ala Met Asp Val Ala Gly Glu Gln Gln		
25	85	90	95
	Leu Asp Val Glu His Asn Leu Phe Lys Gln Arg Leu Asp Lys Asp Gly		
	100	105	110
	Ile Pro Val Ser Ser Glu Ala Glu Arg His Glu Leu Gly Lys Val Glu		
	115	120	125
	285		

Val Thr Val Phe Asp Pro Asp Ser Leu Asp Pro Asp Arg Cys Glu Ser  
130 135 140  
Cys Tyr Gly Ala Glu Ala Glu Asp Ile Lys Cys Cys Asn Thr Cys Glu  
145 150 155 160  
5 Asp Val Arg Glu Ala Tyr Arg Arg Arg Gly Trp Ala Phe Lys Asn Pro  
165 170 175  
Asp Thr Ile Glu Gln Cys Arg Arg Glu Gly Phe Ser Gln Lys Met Gln  
180 185 190  
Glu Gln Lys Asn Glu Gly Cys Gln Val Tyr Gly Phe Leu Glu Val Asn  
10 195 200 205  
Lys Val Ala Gly Asn Phe His Phe Ala Pro Gly Lys Ser Phe Gln Gln  
210 215 220  
Ser His Val His Val His Asp Leu Gln Ser Phe Gly Leu Asp Asn Ile  
225 230 235 240  
15 Asn Met Thr His Tyr Ile Gln His Leu Ser Phe Gly Glu Asp Tyr Pro  
245 250 255  
Gly Ile Val Asn Pro Leu Asp His Thr Asn Val Thr Ala Pro Gln Ala  
260 265 270  
Ser Met Met Phe Gln Tyr Phe Val Lys Val Val Pro Thr Val Tyr Met  
20 275 280 285  
Lys Val Asp Gly Glu Val Leu Arg Thr Asn Gln Phe Ser Val Thr Arg  
290 295 300  
His Glu Lys Val Ala Asn Gly Leu Leu Gly Asp Gln Gly Leu Pro Gly  
305 310 315 320  
25 Val Phe Val Leu Tyr Glu Leu Ser Pro Met Met Val Lys Leu Thr Glu  
325 330 335  
Lys His Arg Ser Phe Thr His Phe Leu Thr Gly Val Cys Ala Ile Ile  
340 345 350  
Gly Gly Met Phe Thr Val Ala Gly Leu Ile Asp Ser Leu Ile Tyr His  
286

355                      360                      365  
 Ser Ala Arg Ala Ile Gln Lys Lys Ile Asp Leu Gly Lys Thr Thr  
 370                      375                      380  
  
 5  
 <210> 89  
 <211> 391  
 <212> PRT  
 <213> Homo sapiens  
  
 10  
 <400> 89  
 Met Ala Asp Ile Asp Asn Lys Glu Gln Ser Glu Leu Asp Gln Asp Leu  
 1                      5                      10                      15  
 Asp Asp Val Glu Glu Val Glu Glu Glu Glu Thr Gly Glu Glu Thr Lys  
 15                      20                      25                      30  
 Leu Lys Ala Arg Gln Leu Thr Val Gln Met Met Gln Asn Pro Gln Ile  
 35                      40                      45  
 Leu Ala Ala Leu Gln Glu Arg Leu Asp Gly Leu Val Glu Thr Pro Thr  
 50                      55                      60  
 20 Gly Tyr Ile Glu Ser Leu Pro Arg Val Val Lys Arg Arg Val Asn Ala  
 65                      70                      75                      80  
 Leu Lys Asn Leu Gln Val Lys Cys Ala Gln Ile Glu Ala Lys Phe Tyr  
 85                      90                      95  
 Glu Glu Val His Asp Leu Glu Arg Lys Tyr Ala Val Leu Tyr Gln Pro  
 25                      100                      105                      110  
 Leu Phe Asp Lys Arg Phe Glu Ile Ile Asn Ala Ile Tyr Glu Pro Thr  
 115                      120                      125  
 Glu Glu Glu Cys Glu Trp Lys Pro Asp Glu Glu Asp Glu Ile Ser Glu  
 130                      135                      140  
 287

Glu Leu Lys Glu Lys Ala Lys Ile Glu Asp Glu Lys Lys Asp Glu Glu  
 145                      150                      155                      160  
 Lys Glu Asp Pro Lys Gly Ile Pro Glu Phe Trp Leu Thr Val Phe Lys  
                          165                      170                      175  
 5 Asn Val Asp Leu Leu Ser Asp Met Val Gln Glu His Asp Glu Pro Ile  
                          180                      185                      190  
 Leu Lys His Leu Lys Asp Ile Lys Val Lys Phe Ser Asp Ala Gly Gln  
                          195                      200                      205  
 Pro Met Ser Phe Val Leu Glu Phe His Phe Glu Pro Asn Glu Tyr Phe  
 10                      210                      215                      220  
 Thr Asn Glu Val Leu Thr Lys Thr Tyr Arg Met Arg Ser Glu Pro Asp  
 225                      230                      235                      240  
 Asp Ser Asp Pro Phe Ser Phe Asp Gly Pro Glu Ile Met Gly Cys Thr  
                          245                      250                      255  
 15 Gly Cys Gln Ile Asp Trp Lys Lys Gly Lys Asn Val Thr Leu Lys Thr  
                          260                      265                      270  
 Ile Lys Lys Lys Gln Lys His Lys Gly Arg Gly Thr Val Arg Thr Val  
                          275                      280                      285  
 Thr Lys Thr Val Ser Asn Asp Ser Phe Phe Asn Phe Phe Ala Pro Pro  
 20                      290                      295                      300  
 Glu Val Pro Glu Ser Gly Asp Leu Asp Asp Asp Ala Glu Ala Ile Leu  
 305                      310                      315                      320  
 Ala Ala Asp Phe Glu Ile Gly His Phe Leu Arg Glu Arg Ile Ile Pro  
                          325                      330                      335  
 25 Arg Ser Val Leu Tyr Phe Thr Gly Glu Ala Ile Glu Asp Asp Asp Asp  
                          340                      345                      350  
 Asp Tyr Asp Glu Glu Gly Glu Glu Ala Asp Glu Glu Gly Glu Glu Glu  
                          355                      360                      365  
 Gly Asp Glu Glu Asn Asp Pro Asp Tyr Asp Pro Lys Lys Asp Gln Asn  
 288

370

375

380

Pro Ala Glu Cys Lys Gln Gln

385

390

5

&lt;210&gt; 90

&lt;211&gt; 836

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

10

&lt;400&gt; 90

Met Ile Pro Phe Leu Pro Met Phe Ser Leu Leu Leu Leu Leu Ile Val

1

5

10

15

Asn Pro Ile Asn Ala Asn Asn His Tyr Asp Lys Ile Leu Ala His Ser

15

20

25

30

Arg Ile Arg Gly Arg Asp Gln Gly Pro Asn Val Cys Ala Leu Gln Gln

35

40

45

Ile Leu Gly Thr Lys Lys Lys Tyr Phe Ser Thr Cys Lys Asn Trp Tyr

50

55

60

20 Lys Lys Ser Ile Cys Gly Gln Lys Thr Thr Val Leu Tyr Glu Cys Cys

65

70

75

80

Pro Gly Tyr Met Arg Met Glu Gly Met Lys Gly Cys Pro Ala Val Leu

85

90

95

Pro Ile Asp His Val Tyr Gly Thr Leu Gly Ile Val Gly Ala Thr Thr

25

100

105

110

Thr Gln Arg Tyr Ser Asp Ala Ser Lys Leu Arg Glu Glu Ile Glu Gly

115

120

125

Lys Gly Ser Phe Thr Tyr Phe Ala Pro Ser Asn Glu Ala Trp Asp Asn

130

135

140

289

[illegible]

	370	375	380	
	Thr Asp Leu Val Ala Gln Leu Gly Leu Ala Ser Ala Leu Arg Pro Asp			
	385	390	395	400
	Gly Glu Tyr Thr Leu Leu Ala Pro Val Asn Asn Ala Phe Ser Asp Asp			
5	405	410	415	
	Thr Leu Ser Met Val Gln Arg Leu Leu Lys Leu Ile Leu Gln Asn His			
	420	425	430	
	Ile Leu Lys Val Lys Val Gly Leu Asn Glu Leu Tyr Asn Gly Gln Ile			
	435	440	445	
10	Leu Glu Thr Ile Gly Gly Lys Gln Leu Arg Val Phe Val Tyr Arg Thr			
	450	455	460	
	Ala Val Cys Ile Glu Asn Ser Cys Met Glu Lys Gly Ser Lys Gln Gly			
	465	470	475	480
	Arg Asn Gly Ala Ile His Ile Phe Arg Glu Ile Ile Lys Pro Ala Glu			
15	485	490	495	
	Lys Ser Leu His Glu Lys Leu Lys Gln Asp Lys Arg Phe Ser Thr Phe			
	500	505	510	
	Leu Ser Leu Leu Glu Ala Ala Asp Leu Lys Glu Leu Leu Thr Gln Pro			
	515	520	525	
20	Gly Asp Trp Thr Leu Phe Val Pro Thr Asn Asp Ala Phe Lys Gly Met			
	530	535	540	
	Thr Ser Glu Glu Lys Glu Ile Leu Ile Arg Asp Lys Asn Ala Leu Gln			
	545	550	555	560
	Asn Ile Ile Leu Tyr His Leu Thr Pro Gly Val Phe Ile Gly Lys Gly			
25	565	570	575	
	Phe Glu Pro Gly Val Thr Asn Ile Leu Lys Thr Thr Gln Gly Ser Lys			
	580	585	590	
	Ile Phe Leu Lys Glu Val Asn Asp Thr Leu Leu Val Asn Glu Leu Lys			
	595	600	605	



Ser Lys Glu Ser Asp Ile Met Thr Thr Asn Gly Val Ile His Val Val  
 610 615 620  
 Asp Lys Leu Leu Tyr Pro Ala Asp Thr Pro Val Gly Asn Asp Gln Leu  
 625 630 635 640  
 5. Leu Glu Ile Leu Asn Lys Leu Ile Lys Tyr Ile Gln Ile Lys Phe Val  
 645 650 655  
 Arg Gly Ser Thr Phe Lys Glu Ile Pro Val Thr Val Tyr Thr Thr Lys  
 660 665 670  
 Ile Ile Thr Lys Val Val Glu Pro Lys Ile Lys Val Ile Glu Gly Ser  
 10 675 680 685  
 Leu Gln Pro Ile Ile Lys Thr Glu Gly Pro Thr Leu Thr Lys Val Lys  
 690 695 700  
 Ile Glu Gly Glu Pro Glu Phe Arg Leu Ile Lys Glu Gly Glu Thr Ile  
 705 710 715 720  
 15 Thr Glu Val Ile His Gly Glu Pro Ile Ile Lys Lys Tyr Thr Lys Ile  
 725 730 735  
 Ile Asp Gly Val Pro Val Glu Ile Thr Glu Lys Glu Thr Arg Glu Glu  
 740 745 750  
 Arg Ile Ile Thr Gly Pro Glu Ile Lys Tyr Thr Arg Ile Ser Thr Gly  
 20 755 760 765  
 Gly Gly Glu Thr Glu Glu Thr Leu Lys Lys Leu Leu Gln Glu Glu Val  
 770 775 780  
 Thr Lys Val Thr Lys Phe Ile Glu Gly Gly Asp Gly His Leu Phe Glu  
 785 790 795 800  
 25 Asp Glu Glu Ile Lys Arg Leu Leu Gln Gly Asp Thr Pro Val Arg Lys  
 805 810 815  
 Leu Gln Ala Asn Lys Lys Val Gln Gly Ser Arg Arg Arg Leu Arg Glu  
 820 825 830  
 Gly Arg Ser Gln

&lt;210&gt; 91

5 &lt;211&gt; 3176

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 91

10 Met Arg Lys His Arg His Leu Pro Leu Val Ala Val Phe Cys Leu Phe  
     1                  5                  10                  15  
 Leu Ser Gly Phe Pro Thr Thr His Ala Gln Gln Gln Gln Ala Asp Val  
                   20                  25                  30  
 Lys Asn Gly Ala Ala Ala Asp Ile Ile Phe Leu Val Asp Ser Ser Trp  
 15          35                  40                  45  
 Thr Ile Gly Glu Glu His Phe Gln Leu Val Arg Glu Phe Leu Tyr Asp  
     50                  55                  60  
 Val Val Lys Ser Leu Ala Val Gly Glu Asn Asp Phe His Phe Ala Leu  
     65                  70                  75                  80  
 20 Val Gln Phe Asn Gly Asn Pro His Thr Glu Phe Leu Leu Asn Thr Tyr  
                   85                  90                  95  
 Arg Thr Lys Gln Glu Val Leu Ser His Ile Ser Asn Met Ser Tyr Ile  
                   100                  105                  110  
 Gly Gly Thr Asn Gln Thr Gly Lys Gly Leu Glu Tyr Ile Met Gln Ser  
 25          115                  120                  125  
 His Leu Thr Lys Ala Ala Gly Ser Arg Ala Gly Asp Gly Val Pro Gln  
     130                  135                  140  
 Val Ile Val Val Leu Thr Asp Gly His Ser Lys Asp Gly Leu Ala Leu  
     145                  150                  155                  160  
   293

Pro Ser Ala Glu Leu Lys Ser Ala Asp Val Asn Val Phe Ala Ile Gly  
 165 170 175  
 Val Glu Asp Ala Asp Glu Gly Ala Leu Lys Glu Ile Ala Ser Glu Pro  
 180 185 190  
 5 Leu Asn Met His Met Phe Asn Leu Glu Asn Phe Thr Ser Leu His Asp  
 195 200 205  
 Ile Val Gly Asn Leu Val Ser Cys Val His Ser Ser Val Ser Pro Glu  
 210 215 220  
 Arg Ala Gly Asp Thr Glu Thr Leu Lys Asp Ile Thr Ala Gln Asp Ser  
 10 225 230 235 240  
 Ala Asp Ile Ile Phe Leu Ile Asp Gly Ser Asn Asn Thr Gly Ser Val  
 245 250 255  
 Asn Phe Ala Val Ile Leu Asp Phe Leu Val Asn Leu Leu Glu Lys Leu  
 260 265 270  
 15 Pro Ile Gly Thr Gln Gln Ile Arg Val Gly Val Val Gln Phe Ser Asp  
 275 280 285  
 Glu Pro Arg Thr Met Phe Ser Leu Asp Thr Tyr Ser Thr Lys Ala Gln  
 290 295 300  
 Val Leu Gly Ala Val Lys Ala Leu Gly Phe Ala Gly Gly Glu Leu Ala  
 20 305 310 315 320  
 Asn Ile Gly Leu Ala Leu Asp Phe Val Val Glu Asn His Phe Thr Arg  
 325 330 335  
 Ala Gly Gly Ser Arg Val Glu Glu Gly Val Pro Gln Val Leu Val Leu  
 340 345 350  
 25 Ile Ser Ala Gly Pro Ser Ser Asp Glu Ile Arg Tyr Gly Val Val Ala  
 355 360 365  
 Leu Lys Gln Ala Ser Val Phe Ser Phe Gly Leu Gly Ala Gln Ala Ala  
 370 375 380  
 Ser Arg Ala Glu Leu Gln His Ile Ala Thr Asp Asp Asn Leu Val Phe  
 294

	385	390	395	400
	Thr Val Pro Glu Phe Arg Ser Phe Gly Asp Leu Gln Glu Lys Leu Leu			
	405		410	415
	Pro Tyr Ile Val Gly Val Ala Gln Arg His Ile Val Leu Lys Pro Pro			
5	420	425	430	
	Thr Ile Val Thr Gln Val Ile Glu Val Asn Lys Arg Asp Ile Val Phe			
	435	440	445	
	Leu Val Asp Gly Ser Ser Ala Leu Gly Leu Ala Asn Phe Asn Ala Ile			
	450	455	460	
10	Arg Asp Phe Ile Ala Lys Val Ile Gln Arg Leu Glu Ile Gly Gln Asp			
	465	470	475	480
	Leu Ile Gln Val Ala Val Ala Gln Tyr Ala Asp Thr Val Arg Pro Glu			
	485	490	495	
	Phe Tyr Phe Asn Thr His Pro Thr Lys Arg Glu Val Ile Thr Ala Val			
15	500	505	510	
	Arg Lys Met Lys Pro Leu Asp Gly Ser Ala Leu Tyr Thr Gly Ser Ala			
	515	520	525	
	Leu Asp Phe Val Arg Asn Asn Leu Phe Thr Ser Ser Ala Gly Tyr Arg			
	530	535	540	
20	Ala Ala Glu Gly Ile Pro Lys Leu Leu Val Leu Ile Thr Gly Gly Lys			
	545	550	555	560
	Ser Leu Asp Glu Ile Ser Gln Pro Ala Gln Glu Leu Lys Arg Ser Ser			
	565	570	575	
	Ile Met Ala Phe Ala Ile Gly Asn Lys Gly Ala Asp Gln Ala Glu Leu			
25	580	585	590	
	Glu Glu Ile Ala Phe Asp Ser Ser Leu Val Phe Ile Pro Ala Glu Phe			
	595	600	605	
	Arg Ala Ala Pro Leu Gln Gly Met Leu Pro Gly Leu Leu Ala Pro Leu			
	610	615	620	

Arg Thr Leu Ser Gly Thr Pro Glu Val His Ser Asn Lys Arg Asp Ile  
 625                      630                      635                      640  
 Ile Phe Leu Leu Asp Gly Ser Ala Asn Val Gly Lys Thr Asn Phe Pro  
                     645                      650                      655  
 5 Tyr Val Arg Asp Phe Val Met Asn Leu Val Asn Ser Leu Asp Ile Gly  
                     660                      665                      670  
 Asn Asp Asn Ile Arg Val Gly Leu Val Gln Phe Ser Asp Thr Pro Val  
                     675                      680                      685  
 Thr Glu Phe Ser Leu Asn Thr Tyr Gln Thr Lys Ser Asp Ile Leu Gly  
 10                      690                      695                      700  
 His Leu Arg Gln Leu Gln Leu Gln Gly Gly Ser Gly Leu Asn Thr Gly  
 705                      710                      715                      720  
 Ser Ala Leu Ser Tyr Val Tyr Ala Asn His Phe Thr Glu Ala Gly Gly  
                     725                      730                      735  
 15 Ser Arg Ile Arg Glu His Val Pro Gln Leu Leu Leu Leu Leu Thr Ala  
                     740                      745                      750  
 Gly Gln Ser Glu Asp Ser Tyr Leu Gln Ala Ala Asn Ala Leu Thr Arg  
                     755                      760                      765  
 Ala Gly Ile Leu Thr Phe Cys Val Gly Ala Ser Gln Ala Asn Lys Ala  
 20                      770                      775                      780  
 Glu Leu Glu Gln Ile Ala Phe Asn Pro Ser Leu Val Tyr Leu Met Asp  
 785                      790                      795                      800  
 Asp Phe Ser Ser Leu Pro Ala Leu Pro Gln Gln Leu Ile Gln Pro Leu  
                     805                      810                      815  
 25 Thr Thr Tyr Val Ser Gly Gly Val Glu Glu Val Pro Leu Ala Gln Pro  
                     820                      825                      830  
 Glu Ser Lys Arg Asp Ile Leu Phe Leu Phe Asp Gly Ser Ala Asn Leu  
                     835                      840                      845  
 Val Gly Gln Phe Pro Val Val Arg Asp Phe Leu Tyr Lys Ile Ile Asp  
 296

	850	855	860	
	Glu Leu Asn Val Lys Pro Glu Gly Thr Arg Ile Ala Val Ala Gln Tyr			
	865	870	875	880
	Ser Asp Asp Val Lys Val Glu Ser Arg Phe Asp Glu His Gln Ser Lys			
5	885	890	895	
	Pro Glu Ile Leu Asn Leu Val Lys Arg Met Lys Ile Lys Thr Gly Lys			
	900	905	910	
	Ala Leu Asn Leu Gly Tyr Ala Leu Asp Tyr Ala Gln Arg Tyr Ile Phe			
	915	920	925	
10	Val Lys Ser Ala Gly Ser Arg Ile Glu Asp Gly Val Leu Gln Phe Leu			
	930	935	940	
	Val Leu Leu Val Ala Gly Arg Ser Ser Asp Arg Val Asp Gly Pro Ala			
	945	950	955	960
	Ser Asn Leu Lys Gln Ser Gly Val Val Pro Phe Ile Phe Gln Ala Lys			
15	965	970	975	
	Asn Ala Asp Pro Ala Glu Leu Glu Gln Ile Val Leu Ser Pro Ala Phe			
	980	985	990	
	Ile Leu Ala Ala Glu Ser Leu Pro Lys Ile Gly Asp Leu His Pro Gln			
	995	1000	1005	
20	Ile Val Asn Leu Leu Lys Ser Val His Asn Gly Ala Pro Ala Pro Val			
	1010	1015	1020	
	Ser Gly Glu Lys Asp Val Val Phe Leu Leu Asp Gly Ser Glu Gly Val			
	1025	1030	1035	1040
	Arg Ser Gly Phe Pro Leu Leu Lys Glu Phe Val Gln Arg Val Val Glu			
25	1045	1050	1055	
	Ser Leu Asp Val Gly Gln Asp Arg Val Arg Val Ala Val Val Gln Tyr			
	1060	1065	1070	
	Ser Asp Arg Thr Arg Pro Glu Phe Tyr Leu Asn Ser Tyr Met Asn Lys			
	1075	1080	1085	

Gln Asp Val Val Asn Ala Val Arg Gln Leu Thr Leu Leu Gly Gly Pro  
 1090 1095 1100  
 Thr Pro Asn Thr Gly Ala Ala Leu Glu Phe Val Leu Arg Asn Ile Leu  
 1105 1110 1115 1120  
 5 Val Ser Ser Ala Gly Ser Arg Ile Thr Glu Gly Val Pro Gln Leu Leu  
 1125 1130 1135  
 Ile Val Leu Thr Ala Asp Arg Ser Gly Asp Asp Val Arg Asn Pro Ser  
 1140 1145 1150  
 Val Val Val Lys Arg Gly Gly Ala Val Pro Ile Gly Ile Gly Ile Gly  
 10 1155 1160 1165  
 Asn Ala Asp Ile Thr Glu Met Gln Thr Ile Ser Phe Ile Pro Asp Phe  
 1170 1175 1180  
 Ala Val Ala Ile Pro Thr Phe Arg Gln Leu Gly Thr Val Gln Gln Val  
 1185 1190 1195 1200  
 15 Ile Ser Glu Arg Val Thr Gln Leu Thr Arg Glu Glu Leu Ser Arg Leu  
 1205 1210 1215  
 Gln Pro Val Leu Gln Pro Leu Pro Ser Pro Gly Val Gly Gly Lys Arg  
 1220 1225 1230  
 Asp Val Val Phe Leu Ile Asp Gly Ser Gln Ser Ala Gly Pro Glu Phe  
 20 1235 1240 1245  
 Gln Tyr Val Arg Thr Leu Ile Glu Arg Leu Val Asp Tyr Leu Asp Val  
 1250 1255 1260  
 Gly Phe Asp Thr Thr Arg Val Ala Val Ile Gln Phe Ser Asp Asp Pro  
 1265 1270 1275 1280  
 25 Lys Ala Glu Phe Leu Leu Asn Ala His Ser Ser Lys Asp Glu Val Gln  
 1285 1290 1295  
 Asn Ala Val Gln Arg Leu Arg Pro Lys Gly Gly Arg Gln Ile Asn Val  
 1300 1305 1310  
 Gly Asn Ala Leu Glu Tyr Val Ser Arg Asn Ile Phe Lys Arg Pro Leu  
 298

	1315	1320	1325
	Gly Ser Arg Ile Glu Glu Gly Val Pro Gln Phe Leu Val Leu Ile Ser		
	1330	1335	1340
	Ser Gly Lys Ser Asp Asp Glu Val Val Val Pro Ala Val Glu Leu Lys		
5	1345	1350	1355
	Gln Phe Gly Val Ala Pro Phe Thr Ile Ala Arg Asn Ala Asp Gln Glu		
	1365	1370	1375
	Glu Leu Val Lys Ile Ser Leu Ser Pro Glu Tyr Val Phe Ser Val Ser		
	1380	1385	1390
10	Thr Phe Arg Glu Leu Pro Ser Leu Glu Gln Lys Leu Leu Thr Pro Ile		
	1395	1400	1405
	Thr Thr Leu Thr Ser Glu Gln Ile Gln Lys Leu Leu Ala Ser Thr Arg		
	1410	1415	1420
	Tyr Pro Pro Pro Ala Val Glu Ser Asp Ala Ala Asp Ile Val Phe Leu		
15	1425	1430	1435
	Ile Asp Ser Ser Glu Gly Val Arg Pro Asp Gly Phe Ala His Ile Arg		
	1445	1450	1455
	Asp Phe Val Ser Arg Ile Val Arg Arg Leu Asn Ile Gly Pro Ser Lys		
	1460	1465	1470
20	Val Arg Val Gly Val Val Gln Phe Ser Asn Asp Val Phe Pro Glu Phe		
	1475	1480	1485
	Tyr Leu Lys Thr Tyr Arg Ser Gln Ala Pro Val Leu Asp Ala Ile Arg		
	1490	1495	1500
	Arg Leu Arg Leu Arg Gly Gly Ser Pro Leu Asn Thr Gly Lys Ala Leu		
25	1505	1510	1515
	Glu Phe Val Ala Arg Asn Leu Phe Val Lys Ser Ala Gly Ser Arg Ile		
	1525	1530	1535
	Glu Asp Gly Val Pro Gln His Leu Val Leu Val Leu Gly Gly Lys Ser		
	1540	1545	1550



Gln Asp Asp Val Ser Arg Phe Ala Gln Val Ile Arg Ser Ser Gly Ile  
 1555 1560 1565  
 Val Ser Leu Gly Val Gly Asp Arg Asn Ile Asp Arg Thr Glu Leu Gln  
 1570 1575 1580  
 5 Thr Ile Thr Asn Asp Pro Arg Leu Val Phe Thr Val Arg Glu Phe Arg  
 1585 1590 1595 1600  
 Glu Leu Pro Asn Ile Glu Glu Arg Ile Met Asn Ser Phe Gly Pro Ser  
 1605 1610 1615  
 Ala Ala Thr Pro Ala Pro Pro Gly Val Asp Thr Pro Pro Pro Ser Arg  
 10 1620 1625 1630  
 Pro Glu Lys Lys Lys Ala Asp Ile Val Phe Leu Leu Asp Gly Ser Ile  
 1635 1640 1645  
 Asn Phe Arg Arg Asp Ser Phe Gln Glu Val Leu Arg Phe Val Ser Glu  
 1650 1655 1660  
 15 Ile Val Asp Thr Val Tyr Glu Asp Gly Asp Ser Ile Gln Val Gly Leu  
 1665 1670 1675 1680  
 Val Gln Tyr Asn Ser Asp Pro Thr Asp Glu Phe Phe Leu Lys Asp Phe  
 1685 1690 1695  
 Ser Thr Lys Arg Gln Ile Ile Asp Ala Ile Asn Lys Val Val Tyr Lys  
 20 1700 1705 1710  
 Gly Gly Arg His Ala Asn Thr Lys Val Gly Leu Glu His Leu Arg Val  
 1715 1720 1725  
 Asn His Phe Val Pro Glu Ala Gly Ser Arg Leu Asp Gln Arg Val Pro  
 1730 1735 1740  
 25 Gln Ile Ala Phe Val Ile Thr Gly Gly Lys Ser Val Glu Asp Ala Gln  
 1745 1750 1755 1760  
 Asp Val Ser Leu Ala Leu Thr Gln Arg Gly Val Lys Val Phe Ala Val  
 1765 1770 1775  
 Gly Val Arg Asn Ile Asp Ser Glu Glu Val Gly Lys Ile Ala Ser Asn  
 300

	1780	1785	1790	
	Ser Ala Thr Ala Phe Arg Val Gly Asn Val Gln Glu Leu Ser Glu Leu			
	1795	1800	1805	
	Ser Glu Gln Val Leu Glu Thr Leu His Asp Ala Met His Glu Thr Leu			
5	1810	1815	1820	
	Cys Pro Gly Val Thr Asp Ala Ala Lys Ala Cys Asn Leu Asp Val Ile			
	1825	1830	1835	1840
	Leu Gly Phe Asp Gly Ser Arg Asp Gln Asn Val Phe Val Ala Gln Lys			
	1845	1850	1855	
10	Gly Phe Glu Ser Lys Val Asp Ala Ile Leu Asn Arg Ile Ser Gln Met			
	1860	1865	1870	
	His Arg Val Ser Cys Ser Gly Gly Arg Ser Pro Thr Val Arg Val Ser			
	1875	1880	1885	
	Val Val Ala Asn Thr Pro Ser Gly Pro Val Glu Ala Phe Asp Phe Asp			
15	1890	1895	1900	
	Glu Tyr Gln Pro Glu Met Leu Glu Lys Phe Arg Asn Met Arg Ser Gln			
	1905	1910	1915	1920
	His Pro Tyr Val Leu Thr Glu Asp Thr Leu Lys Val Tyr Leu Asn Lys			
	1925	1930	1935	
20	Phe Arg Gln Ser Ser Pro Asp Ser Val Lys Val Val Ile His Phe Thr			
	1940	1945	1950	
	Asp Gly Ala Asp Gly Asp Leu Ala Asp Leu His Arg Ala Ser Glu Asn			
	1955	1960	1965	
	Leu Arg Gln Glu Gly Val Arg Ala Leu Ile Leu Val Gly Leu Glu Arg			
25	1970	1975	1980	
	Val Val Asn Leu Glu Arg Leu Met His Leu Glu Phe Gly Arg Gly Phe			
	1985	1990	1995	2000
	Met Tyr Asp Arg Pro Leu Arg Leu Asn Leu Leu Asp Leu Asp Tyr Glu			
	2005	2010	2015	

Leu Ala Glu Gln Leu Asp Asn Ile Ala Glu Lys Ala Cys Cys Gly Val  
 2020 2025 2030  
 Pro Cys Lys Cys Ser Gly Gln Arg Gly Asp Arg Gly Pro Ile Gly Ser  
 2035 2040 2045  
 5 Ile Gly Pro Lys Gly Ile Pro Gly Glu Asp Gly Tyr Arg Gly Tyr Pro  
 2050 2055 2060  
 Gly Asp Glu Gly Gly Pro Gly Glu Arg Gly Pro Pro Gly Val Asn Gly  
 2065 2070 2075 2080  
 Thr Gln Gly Phe Gln Gly Cys Pro Gly Gln Arg Gly Val Lys Gly Ser  
 10 2085 2090 2095  
 Arg Gly Phe Pro Gly Glu Lys Gly Glu Val Gly Glu Ile Gly Leu Asp  
 2100 2105 2110  
 Gly Leu Asp Gly Glu Asp Gly Asp Lys Gly Leu Pro Gly Ser Ser Gly  
 2115 2120 2125  
 15 Glu Lys Gly Asn Pro Gly Arg Arg Gly Asp Lys Gly Pro Arg Gly Glu  
 2130 2135 2140  
 Lys Gly Glu Arg Gly Asp Val Gly Ile Arg Gly Asp Pro Gly Asn Pro  
 2145 2150 2155 2160  
 Gly Gln Asp Ser Gln Glu Arg Gly Pro Lys Gly Glu Thr Gly Asp Leu  
 20 2165 2170 2175  
 Gly Pro Met Gly Val Pro Gly Arg Asp Gly Val Pro Gly Gly Pro Gly  
 2180 2185 2190  
 Glu Thr Gly Lys Asn Gly Gly Phe Gly Arg Arg Gly Pro Pro Gly Ala  
 2195 2200 2205  
 25 Lys Gly Asn Lys Gly Gly Pro Gly Gln Pro Gly Phe Glu Gly Glu Gln  
 2210 2215 2220  
 Gly Thr Arg Gly Ala Gln Gly Pro Ala Gly Pro Ala Gly Pro Pro Gly  
 2225 2230 2235 2240  
 Leu Ile Gly Glu Gln Gly Ile Ser Gly Pro Arg Gly Ser Gly Gly Ala

	2245	2250	2255
	Arg Gly Ala Pro Gly Glu Arg Gly Arg Thr Gly Pro Leu Gly Arg Lys		
	2260	2265	2270
	Gly Glu Pro Gly Glu Pro Gly Pro Lys Gly Gly Ile Gly Asn Pro Gly		
5	2275	2280	2285
	Pro Arg Gly Glu Thr Gly Asp Asp Gly Arg Asp Gly Val Gly Ser Glu		
	2290	2295	2300
	Gly Arg Arg Gly Lys Lys Gly Glu Arg Gly Phe Pro Gly Tyr Pro Gly		
	2305	2310	2315
			2320
10	Pro Lys Gly Asn Pro Gly Glu Pro Gly Leu Asn Gly Thr Thr Gly Pro		
	2325	2330	2335
	Lys Gly Ile Arg Gly Arg Arg Gly Asn Ser Gly Pro Pro Gly Ile Val		
	2340	2345	2350
	Gly Gln Lys Gly Arg Pro Gly Tyr Pro Gly Pro Ala Gly Pro Arg Gly		
15	2355	2360	2365
	Asn Arg Gly Asp Ser Ile Asp Gln Cys Ala Leu Ile Gln Ser Ile Lys		
	2370	2375	2380
	Asp Lys Cys Pro Cys Cys Tyr Gly Pro Leu Glu Cys Pro Val Phe Pro		
	2385	2390	2395
			2400
20	Thr Glu Leu Ala Phe Ala Leu Asp Thr Ser Glu Gly Val Asn Gln Asp		
	2405	2410	2415
	Thr Phe Gly Arg Met Arg Asp Val Val Leu Ser Ile Val Asn Val Leu		
	2420	2425	2430
	Thr Ile Ala Glu Ser Asn Cys Pro Thr Gly Ala Arg Val Ala Val Val		
25	2435	2440	2445
	Thr Tyr Asn Asn Glu Val Thr Thr Glu Ile Arg Phe Ala Asp Ser Lys		
	2450	2455	2460
	Arg Lys Ser Val Leu Leu Asp Lys Ile Lys Asn Leu Gln Val Ala Leu		
	2465	2470	2475
			2480

	Thr Ser Lys Gln Gln Ser Leu Glu Thr Ala Met Ser Phe Val Ala Arg		
	2485	2490	2495
	Asn Thr Phe Lys Arg Val Arg Asn Gly Phe Leu Met Arg Lys Val Ala		
	2500	2505	2510
5	Val Phe Phe Ser Asn Thr Pro Thr Arg Ala Ser Pro Gln Leu Arg Glu		
	2515	2520	2525
	Ala Val Leu Lys Leu Ser Asp Ala Gly Ile Thr Pro Leu Phe Leu Thr		
	2530	2535	2540
	Arg Gln Glu Asp Arg Gln Leu Ile Asn Ala Leu Gln Ile Asn Asn Thr		
10	2545	2550	2555
			2560
	Ala Val Gly His Ala Leu Val Leu Pro Ala Gly Arg Asp Leu Thr Asp		
	2565	2570	2575
	Phe Leu Glu Asn Val Leu Thr Cys His Val Cys Leu Asp Ile Cys Asn		
	2580	2585	2590
15	Ile Asp Pro Ser Cys Gly Phe Gly Ser Trp Arg Pro Ser Phe Arg Asp		
	2595	2600	2605
	Arg Arg Ala Ala Gly Ser Asp Val Asp Ile Asp Met Ala Phe Ile Leu		
	2610	2615	2620
	Asp Ser Ala Glu Thr Thr Thr Leu Phe Gln Phe Asn Glu Met Lys Lys		
20	2625	2630	2635
			2640
	Tyr Ile Ala Tyr Leu Val Arg Gln Leu Asp Met Ser Pro Asp Pro Lys		
	2645	2650	2655
	Ala Ser Gln His Phe Ala Arg Val Ala Val Val Gln His Ala Pro Ser		
	2660	2665	2670
25	Glu Ser Val Asp Asn Ala Ser Met Pro Pro Val Lys Val Glu Phe Ser		
	2675	2680	2685
	Leu Thr Asp Tyr Gly Ser Lys Glu Lys Leu Val Asp Phe Leu Ser Arg		
	2690	2695	2700
	Gly Met Thr Gln Leu Gln Gly Thr Arg Ala Leu Gly Ser Ala Ile Glu		

	2705	2710	2715	2720
	Tyr Thr Ile Glu Asn Val Phe Glu Ser Ala Pro Asn Pro Arg Asp Leu			
	2725	2730	2735	
	Lys Ile Val Val Leu Met Leu Thr Gly Glu Val Pro Glu Gln Gln Leu			
5	2740	2745	2750	
	Glu Glu Ala Gln Arg Val Ile Leu Gln Ala Lys Cys Lys Gly Tyr Phe			
	2755	2760	2765	
	Phe Val Val Leu Gly Ile Gly Arg Lys Val Asn Ile Lys Glu Val Tyr			
	2770	2775	2780	
10	Thr Phe Ala Ser Glu Pro Asn Asp Val Phe Phe Lys Leu Val Asp Lys			
	2785	2790	2795	2800
	Ser Thr Glu Leu Asn Glu Glu Pro Leu Met Arg Phe Gly Arg Leu Leu			
	2805	2810	2815	
	Pro Ser Phe Val Ser Ser Glu Asn Ala Phe Tyr Leu Ser Pro Asp Ile			
15	2820	2825	2830	
	Arg Lys Gln Cys Asp Trp Phe Gln Gly Asp Gln Pro Thr Lys Asn Leu			
	2835	2840	2845	
	Val Lys Phe Gly His Lys Gln Val Asn Val Pro Asn Asn Val Thr Ser			
	2850	2855	2860	
20	Ser Pro Thr Ser Asn Pro Val Thr Thr Thr Lys Pro Val Thr Thr Thr			
	2865	2870	2875	2880
	Lys Pro Val Thr Thr Thr Thr Lys Pro Val Thr Thr Thr Lys Pro			
	2885	2890	2895	
	Val Thr Ile Ile Asn Gln Pro Ser Val Lys Pro Ala Ala Ala Lys Pro			
25	2900	2905	2910	
	Ala Pro Ala Lys Pro Val Ala Ala Lys Pro Val Ala Thr Lys Thr Ala			
	2915	2920	2925	
	Thr Val Arg Pro Pro Val Ala Val Lys Pro Ala Thr Ala Ala Lys Pro			
	2930	2935	2940	

Val Ala Ala Lys Pro Ala Ala Val Arg Pro Pro Ala Ala Ala Lys  
 2945                      2950                      2955                      2960  
 Pro Val Ala Thr Lys Pro Glu Val Pro Arg Pro Gln Ala Ala Lys Pro  
                          2965                      2970                      2975  
 5    Ala Ala Thr Lys Pro Ala Thr Thr Lys Pro Val Val Lys Met Leu Arg  
                          2980                      2985                      2990  
 Glu Val Gln Val Phe Glu Ile Thr Glu Asn Ser Ala Lys Leu His Trp  
                          2995                      3000                      3005  
 Glu Arg Pro Glu Pro Pro Gly Pro Tyr Phe Tyr Asp Leu Thr Val Thr  
 10           3010                      3015                      3020  
 Ser Ala His Asp Gln Ser Leu Val Leu Lys Gln Asn Leu Thr Val Thr  
 3025                      3030                      3035                      3040  
 Asp Arg Val Ile Gly Gly Leu Leu Ala Gly Gln Thr Tyr His Val Ala  
                          3045                      3050                      3055  
 15    Val Val Cys Tyr Leu Arg Ser Gln Val Arg Ala Thr Tyr His Gly Ser  
                          3060                      3065                      3070  
 Phe Ser Thr Lys Lys Ser Gln Pro Pro Pro Pro Gln Pro Ala Arg Ser  
                          3075                      3080                      3085  
 Ala Ser Ser Ser Thr Ile Asn Leu Met Val Ser Thr Glu Pro Leu Ala  
 20           3090                      3095                      3100  
 Leu Thr Glu Thr Asp Ile Cys Lys Leu Pro Lys Asp Glu Gly Thr Cys  
 3105                      3110                      3115                      3120  
 Arg Asp Phe Ile Leu Lys Trp Tyr Tyr Asp Pro Asn Thr Lys Ser Cys  
                          3125                      3130                      3135  
 25    Ala Arg Phe Trp Tyr Gly Gly Cys Gly Gly Asn Glu Asn Lys Phe Gly  
                          3140                      3145                      3150  
 Ser Gln Lys Glu Cys Glu Lys Val Cys Ala Pro Val Leu Ala Lys Pro  
                          3155                      3160                      3165  
 Gly Val Ile Ser Val Met Gly Thr

3170

3175

<210> 92

5 <211> 303

<212> PRT

<213> Homo sapiens

<400> 92

10 Met Arg Ala Trp Ile Phe Phe Leu Leu Cys Leu Ala Gly Arg Ala Leu  
1 5 10 15  
Ala Ala Pro Gln Gln Glu Ala Leu Pro Asp Glu Thr Glu Val Val Glu  
20 25 30  
Glu Thr Val Ala Glu Val Thr Glu Val Ser Val Gly Ala Asn Pro Val  
15 35 40 45  
Gln Val Glu Val Gly Glu Phe Asp Asp Gly Ala Glu Glu Thr Glu Glu  
50 55 60  
Glu Val Val Ala Glu Asn Pro Cys Gln Asn His His Cys Lys His Gly  
65 70 75 80  
20 Lys Val Cys Glu Leu Asp Glu Asn Asn Thr Pro Met Cys Val Cys Gln  
85 90 95  
Asp Pro Thr Ser Cys Pro Ala Pro Ile Gly Glu Phe Glu Lys Val Cys  
100 105 110  
Ser Asn Asp Asn Lys Thr Phe Asp Ser Ser Cys His Phe Phe Ala Thr  
25 115 120 125  
Lys Cys Thr Leu Glu Gly Thr Lys Lys Gly His Lys Leu His Leu Asp  
130 135 140  
Tyr Ile Gly Pro Cys Lys Tyr Ile Pro Pro Cys Leu Asp Ser Glu Leu  
145 150 155 160

307



Thr Glu Phe Pro Leu Arg Met Arg Asp Trp Leu Lys Asn Val Leu Val  
 165 170 175  
 Thr Leu Tyr Glu Arg Asp Glu Asp Asn Asn Leu Leu Thr Glu Lys Gln  
 180 185 190  
 5 Lys Leu Arg Val Lys Lys Ile His Glu Asn Glu Lys Arg Leu Glu Ala  
 195 200 205  
 Gly Asp His Pro Val Glu Leu Leu Ala Arg Asp Phe Glu Lys Asn Tyr  
 210 215 220  
 Asn Met Tyr Ile Phe Pro Val His Trp Gln Phe Gly Gln Leu Asp Gln  
 10 225 230 235 240  
 His Pro Ile Asp Gly Tyr Leu Ser His Thr Glu Leu Ala Pro Leu Arg  
 245 250 255  
 Ala Pro Leu Ile Pro Met Glu His Cys Thr Thr Arg Phe Phe Glu Thr  
 260 265 270  
 15 Cys Asp Leu Asp Asn Asp Lys Tyr Ile Ala Leu Asp Glu Trp Ala Gly  
 275 280 285  
 Cys Phe Gly Ile Lys Gln Lys Asp Ile Asp Lys Asp Leu Val Ile  
 290 295 300

20

<210> 93

<211> 683

<212> PRT

<213> Homo sapiens

25

<400> 93

Met Ala Leu Phe Val Arg Leu Leu Ala Leu Ala Leu Ala Leu

1

5

10

15

Gly Pro Ala Ala Thr Leu Ala Gly Pro Ala Lys Ser Pro Tyr Gln Leu

308

	20		25		30
	Val Leu Gln His Ser Arg Leu Arg Gly Arg Gln His Gly Pro Asn Val				
	35		40		45
	Cys Ala Val Gln Lys Val Ile Gly Thr Asn Arg Lys Tyr Phe Thr Asn				
5	50		55		60
	Cys Lys Gln Trp Tyr Gln Arg Lys Ile Cys Gly Lys Ser Thr Val Ile				
	65		70		75
	Ser Tyr Glu Cys Cys Pro Gly Tyr Glu Lys Val Pro Gly Glu Lys Gly				
		85		90	
					95
10	Cys Pro Ala Ala Leu Pro Leu Ser Asn Leu Tyr Glu Thr Leu Gly Val				
	100		105		110
	Val Gly Ser Thr Thr Thr Gln Leu Tyr Thr Asp Arg Thr Glu Lys Leu				
	115		120		125
	Arg Pro Glu Met Glu Gly Pro Gly Ser Phe Thr Ile Phe Ala Pro Ser				
15	130		135		140
	Asn Glu Ala Trp Ala Ser Leu Pro Ala Glu Val Leu Asp Ser Leu Val				
	145		150		155
	Ser Asn Val Asn Ile Glu Leu Leu Asn Ala Leu Arg Tyr His Met Val				
		165		170	
					175
20	Gly Arg Arg Val Leu Thr Asp Glu Leu Lys His Gly Met Thr Leu Thr				
	180		185		190
	Ser Met Tyr Gln Asn Ser Asn Ile Gln Ile His His Tyr Pro Asn Gly				
	195		200		205
	Ile Val Thr Val Asn Cys Ala Arg Leu Leu Lys Ala Asp His His Ala				
25	210		215		220
	Thr Asn Gly Val Val His Leu Ile Asp Lys Val Ile Ser Thr Ile Thr				
	225		230		235
	Asn Asn Ile Gln Gln Ile Ile Glu Ile Glu Asp Thr Phe Glu Thr Leu				
		245		250	
					255

Arg Ala Ala Val Ala Ala Ser Gly Leu Asn Thr Met Leu Glu Gly Asn  
 260 265 270  
 Gly Gln Tyr Thr Leu Leu Ala Pro Thr Asn Glu Ala Phe Glu Lys Ile  
 275 280 285  
 5 Pro Ser Glu Thr Leu Asn Arg Ile Leu Gly Asp Pro Glu Ala Leu Arg  
 290 295 300  
 Asp Leu Leu Asn Asn His Ile Leu Lys Ser Ala Met Cys Ala Glu Ala  
 305 310 315 320  
 Ile Val Ala Gly Leu Ser Val Glu Thr Leu Glu Gly Thr Thr Leu Glu  
 10 325 330 335  
 Val Gly Cys Ser Gly Asp Met Leu Thr Ile Asn Gly Lys Ala Ile Ile  
 340 345 350  
 Ser Asn Lys Asp Ile Leu Ala Thr Asn Gly Val Ile His Tyr Ile Asp  
 355 360 365  
 15 Glu Leu Leu Ile Pro Asp Ser Ala Lys Thr Leu Phe Glu Leu Ala Ala  
 370 375 380  
 Glu Ser Asp Val Ser Thr Ala Ile Asp Leu Phe Arg Gln Ala Gly Leu  
 385 390 395 400  
 Gly Asn His Leu Ser Gly Ser Glu Arg Leu Thr Leu Leu Ala Pro Leu  
 20 405 410 415  
 Asn Ser Val Phe Lys Asp Gly Thr Pro Pro Ile Asp Ala His Thr Arg  
 420 425 430  
 Asn Leu Leu Arg Asn His Ile Ile Lys Asp Gln Leu Ala Ser Lys Tyr  
 435 440 445  
 25 Leu Tyr His Gly Gln Thr Leu Glu Thr Leu Gly Gly Lys Lys Leu Arg  
 450 455 460  
 Val Phe Val Tyr Arg Asn Ser Leu Cys Ile Glu Asn Ser Cys Ile Ala  
 465 470 475 480  
 Ala His Asp Lys Arg Gly Arg Tyr Gly Thr Leu Phe Thr Met Asp Arg  
 310

	485	490	495
	Val Leu Thr Pro Pro Met Gly Thr Val Met Asp Val Leu Lys Gly Asp		
	500	505	510
	Asn Arg Phe Ser Met Leu Val Ala Ala Ile Gln Ser Ala Gly Leu Thr		
5	515	520	525
	Glu Thr Leu Asn Arg Glu Gly Val Tyr Thr Val Phe Ala Pro Thr Asn		
	530	535	540
	Glu Ala Phe Arg Ala Leu Pro Pro Arg Glu Arg Ser Arg Leu Leu Gly		
	545	550	555 560
10	Asp Ala Lys Glu Leu Ala Asn Ile Leu Lys Tyr His Ile Gly Asp Glu		
	565	570	575
	Ile Leu Val Ser Gly Gly Ile Gly Ala Leu Val Arg Leu Lys Ser Leu		
	580	585	590
	Gln Gly Asp Lys Leu Glu Val Ser Leu Lys Asn Asn Val Val Ser Val		
15	595	600	605
	Asn Lys Glu Pro Val Ala Glu Pro Asp Ile Met Ala Thr Asn Gly Val		
	610	615	620
	Val His Val Ile Thr Asn Val Leu Gln Pro Pro Ala Asn Arg Pro Gln		
	625	630	635 640
20	Glu Arg Gly Asp Glu Leu Ala Asp Ser Ala Leu Glu Ile Phe Lys Gln		
	645	650	655
	Ala Ser Ala Phe Ser Arg Ala Ser Gln Arg Ser Val Arg Leu Ala Pro		
	660	665	670
	Val Tyr Gln Lys Leu Leu Glu Arg Met Lys His		
25	675	680	

<210> 94

<211> 2355

<212> PRT

<213> Homo sapiens

<400> 94

5 Met Leu Arg Gly Pro Gly Pro Gly Leu Leu Leu Leu Ala Val Gln Cys  
1 5 10 15  
Leu Gly Thr Ala Val Pro Ser Thr Gly Ala Ser Lys Ser Lys Arg Gln  
20 25 30  
Ala Gln Gln Met Val Gln Pro Gln Ser Pro Val Ala Val Ser Gln Ser  
10 35 40 45  
Lys Pro Gly Cys Tyr Asp Asn Gly Lys His Tyr Gln Ile Asn Gln Gln  
50 55 60  
Trp Glu Arg Thr Tyr Leu Gly Asn Ala Leu Val Cys Thr Cys Tyr Gly  
65 70 75 80  
15 Gly Ser Arg Gly Phe Asn Cys Glu Ser Lys Pro Glu Ala Glu Glu Thr  
85 90 95  
Cys Phe Asp Lys Tyr Thr Gly Asn Thr Tyr Arg Val Gly Asp Thr Tyr  
100 105 110  
Glu Arg Pro Lys Asp Ser Met Ile Trp Asp Cys Thr Cys Ile Gly Ala  
20 115 120 125  
Gly Arg Gly Arg Ile Ser Cys Thr Ile Ala Asn Arg Cys His Glu Gly  
130 135 140  
Gly Gln Ser Tyr Lys Ile Gly Asp Thr Trp Arg Arg Pro His Glu Thr  
145 150 155 160  
25 Gly Gly Tyr Met Leu Glu Cys Val Cys Leu Gly Asn Gly Lys Gly Glu  
165 170 175  
Trp Thr Cys Lys Pro Ile Ala Glu Lys Cys Phe Asp His Ala Ala Gly  
180 185 190  
Thr Ser Tyr Val Val Gly Glu Thr Trp Glu Lys Pro Tyr Gln Gly Trp  
312

	195	200	205
	Met Met Val Asp Cys Thr Cys Leu Gly Glu Gly Ser Gly Arg Ile Thr		
	210	215	220
	Cys Thr Ser Arg Asn Arg Cys Asn Asp Gln Asp Thr Arg Thr Ser Tyr		
5	225	230	235 240
	Arg Ile Gly Asp Thr Trp Ser Lys Lys Asp Asn Arg Gly Asn Leu Leu		
	245	250	255
	Gln Cys Ile Cys Thr Gly Asn Gly Arg Gly Glu Trp Lys Cys Glu Arg		
	260	265	270
10	His Thr Ser Val Gln Thr Thr Ser Ser Gly Ser Gly Pro Phe Thr Asp		
	275	280	285
	Val Arg Ala Ala Val Tyr Gln Pro Gln Pro His Pro Gln Pro Pro Pro		
	290	295	300
	Tyr Gly His Cys Val Thr Asp Ser Gly Val Val Tyr Ser Val Gly Met		
15	305	310	315 320
	Gln Trp Leu Lys Thr Gln Gly Asn Lys Gln Met Leu Cys Thr Cys Leu		
	325	330	335
	Gly Asn Gly Val Ser Cys Gln Glu Thr Ala Val Thr Gln Thr Tyr Gly		
	340	345	350
20	Gly Asn Ser Asn Gly Glu Pro Cys Val Leu Pro Phe Thr Tyr Asn Gly		
	355	360	365
	Arg Thr Phe Tyr Ser Cys Thr Thr Glu Gly Arg Gln Asp Gly His Leu		
	370	375	380
	Trp Cys Ser Thr Thr Ser Asn Tyr Glu Gln Asp Gln Lys Tyr Ser Phe		
25	385	390	395 400
	Cys Thr Asp His Thr Val Leu Val Gln Thr Arg Gly Gly Asn Ser Asn		
	405	410	415
	Gly Ala Leu Cys His Phe Pro Phe Leu Tyr Asn Asn His Asn Tyr Thr		
	420	425	430
		313	

Asp Cys Thr Ser Glu Gly Arg Arg Asp Asn Met Lys Trp Cys Gly Thr  
 435 440 445  
 Thr Gln Asn Tyr Asp Ala Asp Gln Lys Phe Gly Phe Cys Pro Met Ala  
 450 455 460  
 5 Ala His Glu Glu Ile Cys Thr Thr Asn Glu Gly Val Met Tyr Arg Ile  
 465 470 475 480  
 Gly Asp Gln Trp Asp Lys Gln His Asp Met Gly His Met Met Arg Cys  
 485 490 495  
 Thr Cys Val Gly Asn Gly Arg Gly Glu Trp Thr Cys Ile Ala Tyr Ser  
 10 500 505 510  
 Gln Leu Arg Asp Gln Cys Ile Val Asp Asp Ile Thr Tyr Asn Val Asn  
 515 520 525  
 Asp Thr Phe His Lys Arg His Glu Glu Gly His Met Leu Asn Cys Thr  
 530 535 540  
 15 Cys Phe Gly Gln Gly Arg Gly Arg Trp Lys Cys Asp Pro Val Asp Gln  
 545 550 555 560  
 Cys Gln Asp Ser Glu Thr Gly Thr Phe Tyr Gln Ile Gly Asp Ser Trp  
 565 570 575  
 Glu Lys Tyr Val His Gly Val Arg Tyr Gln Cys Tyr Cys Tyr Gly Arg  
 20 580 585 590  
 Gly Ile Gly Glu Trp His Cys Gln Pro Leu Gln Thr Tyr Pro Ser Ser  
 595 600 605  
 Ser Gly Pro Val Glu Val Phe Ile Thr Glu Thr Pro Ser Gln Pro Asn  
 610 615 620  
 25 Ser His Pro Ile Gln Trp Asn Ala Pro Gln Pro Ser His Ile Ser Lys  
 625 630 635 640  
 Tyr Ile Leu Arg Trp Arg Pro Lys Asn Ser Val Gly Arg Trp Lys Glu  
 645 650 655  
 Ala Thr Ile Pro Gly His Leu Asn Ser Tyr Thr Ile Lys Gly Leu Lys

	660	665	670
	Pro Gly Val Val Tyr Glu Gly Gln Leu Ile Ser Ile Gln Gln Tyr Gly		
	675	680	685
	His Gln Glu Val Thr Arg Phe Asp Phe Thr Thr Thr Ser Thr Ser Thr		
5	690	695	700
	Pro Val Thr Ser Asn Thr Val Thr Gly Glu Thr Thr Pro Phe Ser Pro		
	705	710	715 720
	Leu Val Ala Thr Ser Glu Ser Val Thr Glu Ile Thr Ala Ser Ser Phe		
	725	730	735
10	Val Val Ser Trp Val Ser Ala Ser Asp Thr Val Ser Gly Phe Arg Val		
	740	745	750
	Glu Tyr Glu Leu Ser Glu Glu Gly Asp Glu Pro Gln Tyr Leu Asp Leu		
	755	760	765
	Pro Ser Thr Ala Thr Ser Val Asn Ile Pro Asp Leu Leu Pro Gly Arg		
15	770	775	780
	Lys Tyr Ile Val Asn Val Tyr Gln Ile Ser Glu Asp Gly Glu Gln Ser		
	785	790	795 800
	Leu Ile Leu Ser Thr Ser Gln Thr Thr Ala Pro Asp Ala Pro Pro Asp		
	805	810	815
20	Pro Thr Val Asp Gln Val Asp Asp Thr Ser Ile Val Val Arg Trp Ser		
	820	825	830
	Arg Pro Gln Ala Pro Ile Thr Gly Tyr Arg Ile Val Tyr Ser Pro Ser		
	835	840	845
	Val Glu Gly Ser Ser Thr Glu Leu Asn Leu Pro Glu Thr Ala Asn Ser		
25	850	855	860
	Val Thr Leu Ser Asp Leu Gln Pro Gly Val Gln Tyr Asn Ile Thr Ile		
	865	870	875 880
	Tyr Ala Val Glu Glu Asn Gln Glu Ser Thr Pro Val Val Ile Gln Gln		
	885	890	895
		315	



Glu Thr Thr Gly Thr Pro Arg Ser Asp Thr Val Pro Ser Pro Arg Asp  
 900 905 910  
 Leu Gln Phe Val Glu Val Thr Asp Val Lys Val Thr Ile Met Trp Thr  
 915 920 925  
 5 Pro Pro Glu Ser Ala Val Thr Gly Tyr Arg Val Asp Val Ile Pro Val  
 930 935 940  
 Asn Leu Pro Gly Glu His Gly Gln Arg Leu Pro Ile Ser Arg Asn Thr  
 945 950 955 960  
 Phe Ala Glu Val Thr Gly Leu Ser Pro Gly Val Thr Tyr Tyr Phe Lys  
 10 965 970 975  
 Val Phe Ala Val Ser His Gly Arg Glu Ser Lys Pro Leu Thr Ala Gln  
 980 985 990  
 Gln Thr Thr Lys Leu Asp Ala Pro Thr Asn Leu Gln Phe Val Asn Glu  
 995 1000 1005  
 15 Thr Asp Ser Thr Val Leu Val Arg Trp Thr Pro Pro Arg Ala Gln Ile  
 1010 1015 1020  
 Thr Gly Tyr Arg Leu Thr Val Gly Leu Thr Arg Arg Gly Gln Pro Arg  
 1025 1030 1035 1040  
 Gln Tyr Asn Val Gly Pro Ser Val Ser Lys Tyr Pro Leu Arg Asn Leu  
 20 1045 1050 1055  
 Gln Pro Ala Ser Glu Tyr Thr Val Ser Leu Val Ala Ile Lys Gly Asn  
 1060 1065 1070  
 Gln Glu Ser Pro Lys Ala Thr Gly Val Phe Thr Thr Leu Gln Pro Gly  
 1075 1080 1085  
 25 Ser Ser Ile Pro Pro Tyr Asn Thr Glu Val Thr Glu Thr Thr Ile Val  
 1090 1095 1100  
 Ile Thr Trp Thr Pro Ala Pro Arg Ile Gly Phe Lys Leu Gly Val Arg  
 1105 1110 1115 1120  
 Pro Ser Gln Gly Gly Glu Ala Pro Arg Glu Val Thr Ser Asp Ser Gly  
 316

	1125	1130	1135
	Ser Ile Val Val Ser Gly Leu Thr Pro Gly Val Glu Tyr Val Tyr Thr		
	1140	1145	1150
	Ile Gln Val Leu Arg Asp Gly Gln Glu Arg Asp Ala Pro Ile Val Asn		
5	1155	1160	1165
	Lys Val Val Thr Pro Leu Ser Pro Pro Thr Asn Leu His Leu Glu Ala		
	1170	1175	1180
	Asn Pro Asp Thr Gly Val Leu Thr Val Ser Trp Glu Arg Ser Thr Thr		
	1185	1190	1195
			1200
10	Pro Asp Ile Thr Gly Tyr Arg Ile Thr Thr Thr Pro Thr Asn Gly Gln		
	1205	1210	1215
	Gln Gly Asn Ser Leu Glu Glu Val Val His Ala Asp Gln Ser Ser Cys		
	1220	1225	1230
	Thr Phe Asp Asn Leu Ser Pro Gly Leu Glu Tyr Asn Val Ser Val Tyr		
15	1235	1240	1245
	Thr Val Lys Asp Asp Lys Glu Ser Val Pro Ile Ser Asp Thr Ile Ile		
	1250	1255	1260
	Pro Ala Val Pro Pro Pro Thr Asp Leu Arg Phe Thr Asn Ile Gly Pro		
	1265	1270	1275
			1280
20	Asp Thr Met Arg Val Thr Trp Ala Pro Pro Pro Ser Ile Asp Leu Thr		
	1285	1290	1295
	Asn Phe Leu Val Arg Tyr Ser Pro Val Lys Asn Glu Glu Asp Val Ala		
	1300	1305	1310
	Glu Leu Ser Ile Ser Pro Ser Asp Asn Ala Val Val Leu Thr Asn Leu		
25	1315	1320	1325
	Leu Pro Gly Thr Glu Tyr Val Val Ser Val Ser Ser Val Tyr Glu Gln		
	1330	1335	1340
	His Glu Ser Thr Pro Leu Arg Gly Arg Gln Lys Thr Gly Leu Asp Ser		
	1345	1350	1355
			1360

Pro Thr Gly Ile Asp Phe Ser Asp Ile Thr Ala Asn Ser Phe Thr Val  
 1365 1370 1375  
 His Trp Ile Ala Pro Arg Ala Thr Ile Thr Gly Tyr Arg Ile Arg His  
 1380 1385 1390  
 5 His Pro Glu His Phe Ser Gly Arg Pro Arg Glu Asp Arg Val Pro His  
 1395 1400 1405  
 Ser Arg Asn Ser Ile Thr Leu Thr Asn Leu Thr Pro Gly Thr Glu Tyr  
 1410 1415 1420  
 Val Val Ser Ile Val Ala Leu Asn Gly Arg Glu Glu Ser Pro Leu Leu  
 10 1425 1430 1435 1440  
 Ile Gly Gln Gln Ser Thr Val Ser Asp Val Pro Arg Asp Leu Glu Val  
 1445 1450 1455  
 Val Ala Ala Thr Pro Thr Ser Leu Leu Ile Ser Trp Asp Ala Pro Ala  
 1460 1465 1470  
 15 Val Thr Val Arg Tyr Tyr Arg Ile Thr Tyr Gly Glu Thr Gly Gly Asn  
 1475 1480 1485  
 Ser Pro Val Gln Glu Phe Thr Val Pro Gly Ser Lys Ser Thr Ala Thr  
 1490 1495 1500  
 Ile Ser Gly Leu Lys Pro Gly Val Asp Tyr Thr Ile Thr Val Tyr Ala  
 20 1505 1510 1515 1520  
 Val Thr Gly Arg Gly Asp Ser Pro Ala Ser Ser Lys Pro Ile Ser Ile  
 1525 1530 1535  
 Asn Tyr Arg Thr Glu Ile Asp Lys Pro Ser Gln Met Gln Val Thr Asp  
 1540 1545 1550  
 25 Val Gln Asp Asn Ser Ile Ser Val Lys Trp Leu Pro Ser Ser Ser Pro  
 1555 1560 1565  
 Val Thr Gly Tyr Arg Val Thr Thr Thr Pro Lys Asn Gly Pro Gly Pro  
 1570 1575 1580  
 Thr Lys Thr Lys Thr Ala Gly Pro Asp Gln Thr Glu Met Thr Ile Glu

	1585	1590	1595	1600
	Gly Leu Gln Pro Thr Val Glu Tyr Val Val Ser Val Tyr Ala Gln Asn			
	1605	1610	1615	
	Pro Ser Gly Glu Ser Gln Pro Leu Val Gln Thr Ala Val Thr Asn Ile			
5	1620	1625	1630	
	Asp Arg Pro Lys Gly Leu Ala Phe Thr Asp Val Asp Val Asp Ser Ile			
	1635	1640	1645	
	Lys Ile Ala Trp Glu Ser Pro Gln Gly Gln Val Ser Arg Tyr Arg Val			
	1650	1655	1660	
10	Thr Tyr Ser Ser Pro Glu Asp Gly Ile His Glu Leu Phe Pro Ala Pro			
	1665	1670	1675	1680
	Asp Gly Glu Glu Asp Thr Ala Glu Leu Gln Gly Leu Arg Pro Gly Ser			
	1685	1690	1695	
	Glu Tyr Thr Val Ser Val Val Ala Leu His Asp Asp Met Glu Ser Gln			
15	1700	1705	1710	
	Pro Leu Ile Gly Thr Gln Ser Thr Ala Ile Pro Ala Pro Thr Asp Leu			
	1715	1720	1725	
	Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro			
	1730	1735	1740	
20	Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu			
	1745	1750	1755	1760
	Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser			
	1765	1770	1775	
	Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val			
25	1780	1785	1790	
	Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val			
	1795	1800	1805	
	Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp			
	1810	1815	1820	

Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr  
 1825                      1830                      1835                      1840  
 Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro  
                          1845                      1850                      1855  
 5 Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly  
                          1860                      1865                      1870  
 Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp  
                          1875                      1880                      1885  
 Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp  
 10                      1890                      1895                      1900  
 Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu  
 1905                      1910                      1915                      1920  
 Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys  
                          1925                      1930                      1935  
 15 Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg  
                          1940                      1945                      1950  
 Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu  
                          1955                      1960                      1965  
 Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro  
 20                      1970                      1975                      1980  
 Leu Ile Gly Arg Lys Lys Thr Asp Glu Leu Pro Gln Leu Val Thr Leu  
 1985                      1990                      1995                      2000  
 Pro His Pro Asn Leu His Gly Pro Glu Ile Leu Asp Val Pro Ser Thr  
                          2005                      2010                      2015  
 25 Val Gln Lys Thr Pro Phe Val Thr His Pro Gly Tyr Asp Thr Gly Asn  
                          2020                      2025                      2030  
 Gly Ile Gln Leu Pro Gly Thr Ser Gly Gln Gln Pro Ser Val Gly Gln  
                          2035                      2040                      2045  
 Gln Met Ile Phe Glu Glu His Gly Phe Arg Arg Thr Thr Pro Pro Thr  
 320

	2050	2055	2060
	Thr Ala Thr Pro Ile Arg His Arg Pro Arg Pro Tyr Pro Pro Asn Val		
	2065	2070	2075 2080
	Gly Gln Glu Ala Leu Ser Gln Thr Thr Ile Ser Trp Ala Pro Phe Gln		
5	2085	2090	2095
	Asp Thr Ser Glu Tyr Ile Ile Ser Cys His Pro Val Gly Thr Asp Glu		
	2100	2105	2110
	Glu Pro Leu Gln Phe Arg Val Pro Gly Thr Ser Thr Ser Ala Thr Leu		
	2115	2120	2125
10	Thr Gly Leu Thr Arg Gly Ala Thr Tyr Asn Ile Ile Val Glu Ala Leu		
	2130	2135	2140
	Lys Asp Gln Gln Arg His Lys Val Arg Glu Glu Val Val Thr Val Gly		
	2145	2150	2155 2160
	Asn Ser Val Asn Glu Gly Leu Asn Gln Pro Thr Asp Asp Ser Cys Phe		
15	2165	2170	2175
	Asp Pro Tyr Thr Val Ser His Tyr Ala Val Gly Asp Glu Trp Glu Arg		
	2180	2185	2190
	Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln Cys Leu Gly Phe Gly		
	2195	2200	2205
20	Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp Cys His Asp Asn Gly		
	2210	2215	2220
	Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly Glu Asn Gly		
	2225	2230	2235 2240
	Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys Gly Glu Phe Lys		
25	2245	2250	2255
	Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp Gly Lys Thr Tyr His		
	2260	2265	2270
	Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly Ala Ile Cys Ser Cys		
	2275	2280	2285

Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys Asp Asn Cys Arg Arg  
 2290 2295 2300  
 Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly Gln Ser Tyr Asn  
 2305 2310 2315 2320  
 5 Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr Asn Val Asn Cys  
 2325 2330 2335  
 Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln Ala Asp Arg Glu Asp  
 2340 2345 2350  
 Ser Arg Glu  
 10 2355

<210> 95

<211> 1366

15 <212> PRT

<213> Homo sapiens

<400> 95

Met Leu Ser Phe Val Asp Thr Arg Thr Leu Leu Leu Leu Ala Val Thr  
 20 1 5 10 15  
 Leu Cys Leu Ala Thr Cys Gln Ser Leu Gln Glu Glu Thr Val Arg Lys  
 20 25 30  
 Gly Pro Ala Gly Asp Arg Gly Pro Arg Gly Glu Arg Gly Pro Pro Gly  
 35 40 45  
 25 Pro Pro Gly Arg Asp Gly Glu Asp Gly Pro Thr Gly Pro Pro Gly Pro  
 50 55 60  
 Pro Gly Pro Pro Gly Pro Pro Gly Leu Gly Gly Asn Phe Ala Ala Gln  
 65 70 75 80  
 Tyr Asp Gly Lys Gly Val Gly Leu Gly Pro Gly Pro Met Gly Leu Met  
 322

	85	90	95
	Gly Pro Arg Gly Pro Pro Gly Ala Ala Gly Ala Pro Gly Pro Gln Gly		
	100	105	110
	Phe Gln Gly Pro Ala Gly Glu Pro Gly Glu Pro Gly Gln Thr Gly Pro		
5	115	120	125
	Ala Gly Ala Arg Gly Pro Ala Gly Pro Pro Gly Lys Ala Gly Glu Asp		
	130	135	140
	Gly His Pro Gly Lys Pro Gly Arg Pro Gly Glu Arg Gly Val Val Gly		
	145	150	155
			160
10	Pro Gln Gly Ala Arg Gly Phe Pro Gly Thr Pro Gly Leu Pro Gly Phe		
	165	170	175
	Lys Gly Ile Arg Gly His Asn Gly Leu Asp Gly Leu Lys Gly Gln Pro		
	180	185	190
	Gly Ala Pro Gly Val Lys Gly Glu Pro Gly Ala Pro Gly Glu Asn Gly		
15	195	200	205
	Thr Pro Gly Gln Thr Gly Ala Arg Gly Leu Pro Gly Glu Arg Gly Arg		
	210	215	220
	Val Gly Ala Pro Gly Pro Ala Gly Ala Arg Gly Ser Asp Gly Ser Val		
	225	230	235
			240
20	Gly Pro Val Gly Pro Ala Gly Pro Ile Gly Ser Ala Gly Pro Pro Gly		
	245	250	255
	Phe Pro Gly Ala Pro Gly Pro Lys Gly Glu Ile Gly Ala Val Gly Asn		
	260	265	270
	Ala Gly Pro Ala Gly Pro Ala Gly Pro Arg Gly Glu Val Gly Leu Pro		
25	275	280	285
	Gly Leu Ser Gly Pro Val Gly Pro Pro Gly Asn Pro Gly Ala Asn Gly		
	290	295	300
	Leu Thr Gly Ala Lys Gly Ala Ala Gly Leu Pro Gly Val Ala Gly Ala		
	305	310	315
			320
		323	



Pro Gly Leu Pro Gly Pro Arg Gly Ile Pro Gly Pro Val Gly Ala Ala  
 325 330 335  
 Gly Ala Thr Gly Ala Arg Gly Leu Val Gly Glu Pro Gly Pro Ala Gly  
 340 345 350  
 5 Ser Lys Gly Glu Ser Gly Asn Lys Gly Glu Pro Gly Ser Ala Gly Pro  
 355 360 365  
 Gln Gly Pro Pro Gly Pro Ser Gly Glu Glu Gly Lys Arg Gly Pro Asn  
 370 375 380  
 Gly Glu Ala Gly Ser Ala Gly Pro Pro Gly Pro Pro Gly Leu Arg Gly  
 10 385 390 395 400  
 Ser Pro Gly Ser Arg Gly Leu Pro Gly Ala Asp Gly Arg Ala Gly Val  
 405 410 415  
 Met Gly Pro Pro Gly Ser Arg Gly Ala Ser Gly Pro Ala Gly Val Arg  
 420 425 430  
 15 Gly Pro Asn Gly Asp Ala Gly Arg Pro Gly Glu Pro Gly Leu Met Gly  
 435 440 445  
 Pro Arg Gly Leu Pro Gly Ser Pro Gly Asn Ile Gly Pro Ala Gly Lys  
 450 455 460  
 Glu Gly Pro Val Gly Leu Pro Gly Ile Asp Gly Arg Pro Gly Pro Ile  
 20 465 470 475 480  
 Gly Pro Ala Gly Ala Arg Gly Glu Pro Gly Asn Ile Gly Phe Pro Gly  
 485 490 495  
 Pro Lys Gly Pro Thr Gly Asp Pro Gly Lys Asn Gly Asp Lys Gly His  
 500 505 510  
 25 Ala Gly Leu Ala Gly Ala Arg Gly Ala Pro Gly Pro Asp Gly Asn Asn  
 515 520 525  
 Gly Ala Gln Gly Pro Pro Gly Pro Gln Gly Val Gln Gly Gly Lys Gly  
 530 535 540  
 Glu Gln Gly Pro Ala Gly Pro Pro Gly Phe Gln Gly Leu Pro Gly Pro  
 324

545                      550                      555                      560  
 Ser Gly Pro Ala Gly Glu Val Gly Lys Pro Gly Glu Arg Gly Leu His  
                          565                      570                      575  
 Gly Glu Phe Gly Leu Pro Gly Pro Ala Gly Pro Arg Gly Glu Arg Gly  
 5                      580                      585                      590  
 Pro Pro Gly Glu Ser Gly Ala Ala Gly Pro Thr Gly Pro Ile Gly Ser  
                          595                      600                      605  
 Arg Gly Pro Ser Gly Pro Pro Gly Pro Asp Gly Asn Lys Gly Glu Pro  
                          610                      615                      620  
 10 Gly Val Val Gly Ala Val Gly Thr Ala Gly Pro Ser Gly Pro Ser Gly  
                          625                      630                      635                      640  
 Leu Pro Gly Glu Arg Gly Ala Ala Gly Ile Pro Gly Gly Lys Gly Glu  
                          645                      650                      655  
 Lys Gly Glu Pro Gly Leu Arg Gly Glu Ile Gly Asn Pro Gly Arg Asp  
 15                      660                      665                      670  
 Gly Ala Arg Gly Ala His Gly Ala Val Gly Ala Pro Gly Pro Ala Gly  
                          675                      680                      685  
 Ala Thr Gly Asp Arg Gly Glu Ala Gly Ala Ala Gly Pro Ala Gly Pro  
                          690                      695                      700  
 20 Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg Gly Glu Val Gly Pro Ala  
                          705                      710                      715                      720  
 Gly Pro Asn Gly Phe Ala Gly Pro Ala Gly Ala Ala Gly Gln Pro Gly  
                          725                      730                      735  
 Ala Lys Gly Glu Arg Gly Ala Lys Gly Pro Lys Gly Glu Asn Gly Val  
 25                      740                      745                      750  
 Val Gly Pro Thr Gly Pro Val Gly Ala Ala Gly Pro Ala Gly Pro Asn  
                          755                      760                      765  
 Gly Pro Pro Gly Pro Ala Gly Ser Arg Gly Asp Gly Gly Pro Pro Gly  
                          770                      775                      780

	Met Thr Gly Phe Pro Gly Ala Ala Gly Arg Thr Gly Pro Pro Gly Pro		
	785	790	795 800
	Ser Gly Ile Ser Gly Pro Pro Gly Pro Pro Gly Pro Ala Gly Lys Glu		
	805	810	815
5	Gly Leu Arg Gly Pro Arg Gly Asp Gln Gly Pro Val Gly Arg Thr Gly		
	820	825	830
	Glu Val Gly Ala Val Gly Pro Pro Gly Phe Ala Gly Glu Lys Gly Pro		
	835	840	845
	Ser Gly Glu Ala Gly Thr Ala Gly Pro Pro Gly Thr Pro Gly Pro Gln		
10	850	855	860
	Gly Leu Leu Gly Ala Pro Gly Ile Leu Gly Leu Pro Gly Ser Arg Gly		
	865	870	875 880
	Glu Arg Gly Leu Pro Gly Val Ala Gly Ala Val Gly Glu Pro Gly Pro		
	885	890	895
15	Leu Gly Ile Ala Gly Pro Pro Gly Ala Arg Gly Pro Pro Gly Ala Val		
	900	905	910
	Gly Ser Pro Gly Val Asn Gly Ala Pro Gly Glu Ala Gly Arg Asp Gly		
	915	920	925
	Asn Pro Gly Asn Asp Gly Pro Pro Gly Arg Asp Gly Gln Pro Gly His		
20	930	935	940
	Lys Gly Glu Arg Gly Tyr Pro Gly Asn Ile Gly Pro Val Gly Ala Ala		
	945	950	955 960
	Gly Ala Pro Gly Pro His Gly Pro Val Gly Pro Ala Gly Lys His Gly		
	965	970	975
25	Asn Arg Gly Glu Thr Gly Pro Ser Gly Pro Val Gly Pro Ala Gly Ala		
	980	985	990
	Val Gly Pro Arg Gly Pro Ser Gly Pro Gln Gly Ile Arg Gly Asp Lys		
	995	1000	1005
	Gly Glu Pro Gly Glu Lys Gly Pro Arg Gly Leu Pro Gly Leu Lys Gly		

	1010	1015	1020
	His Asn Gly Leu Gln Gly Leu Pro Gly Ile Ala Gly His His Gly Asp		
	1025	1030	1035 1040
	Gln Gly Ala Pro Gly Ser Val Gly Pro Ala Gly Pro Arg Gly Pro Ala		
5	1045	1050	1055
	Gly Pro Ser Gly Pro Ala Gly Lys Asp Gly Arg Thr Gly His Pro Gly		
	1060	1065	1070
	Thr Val Gly Pro Ala Gly Ile Arg Gly Pro Gln Gly His Gln Gly Pro		
	1075	1080	1085
10	Ala Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Val Ser		
	1090	1095	1100
	Gly Gly Gly Tyr Asp Phe Gly Tyr Asp Gly Asp Phe Tyr Arg Ala Asp		
	1105	1110	1115 1120
	Gln Pro Arg Ser Ala Pro Ser Leu Arg Pro Lys Asp Tyr Glu Val Asp		
15	1125	1130	1135
	Ala Thr Leu Lys Ser Leu Asn Asn Gln Ile Glu Thr Leu Leu Thr Pro		
	1140	1145	1150
	Glu Gly Ser Arg Lys Asn Pro Ala Arg Thr Cys Arg Asp Leu Arg Leu		
	1155	1160	1165
20	Ser His Pro Glu Trp Ser Ser Gly Tyr Tyr Trp Ile Asp Pro Asn Gln		
	1170	1175	1180
	Gly Cys Thr Met Asp Ala Ile Lys Val Tyr Cys Asp Phe Ser Thr Gly		
	1185	1190	1195 1200
	Glu Thr Cys Ile Arg Ala Gln Pro Glu Asn Ile Pro Ala Lys Asn Trp		
25	1205	1210	1215
	Tyr Arg Ser Ser Lys Asp Lys Lys His Val Trp Leu Gly Glu Thr Ile		
	1220	1225	1230
	Asn Ala Gly Ser Gln Phe Glu Tyr Asn Val Glu Gly Val Thr Ser Lys		
	1235	1240	1245

Glu Met Ala Thr Gln Leu Ala Phe Met Arg Leu Leu Ala Asn Tyr Ala  
 1250 1255 1260  
 Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile Ala Tyr Met Asp  
 1265 1270 1275 1280  
 5 Glu Glu Thr Gly Asn Leu Lys Lys Ala Val Ile Leu Gln Gly Ser Asn  
 1285 1290 1295  
 Asp Val Glu Leu Val Ala Glu Gly Asn Ser Arg Phe Thr Tyr Thr Val  
 1300 1305 1310  
 Leu Val Asp Gly Cys Ser Lys Lys Thr Asn Glu Trp Gly Lys Thr Ile  
 10 1315 1320 1325  
 Ile Glu Tyr Lys Thr Asn Lys Pro Ser Arg Leu Pro Phe Leu Asp Ile  
 1330 1335 1340  
 Ala Pro Leu Asp Ile Gly Gly Ala Asp His Glu Phe Phe Val Asp Ile  
 1345 1350 1355 1360  
 15 Gly Pro Val Cys Phe Lys  
 1365

<210> 96  
 20 <211> 105  
 <212> PRT  
 <213> Homo sapiens

<400> 96  
 25 Met Ala Lys Ile Ser Ser Pro Thr Glu Thr Glu Arg Cys Ile Glu Ser  
 1 5 10 15  
 Leu Ile Ala Val Phe Gln Lys Tyr Ala Gly Lys Asp Gly Tyr Asn Tyr  
 20 25 30  
 Thr Leu Ser Lys Thr Glu Phe Leu Ser Phe Met Asn Thr Glu Leu Ala  
 328

35                      40                      45  
 Ala Phe Thr Lys Asn Gln Lys Asp Pro Gly Val Leu Asp Arg Met Met  
 50                      55                      60  
 Lys Lys Leu Asp Thr Asn Ser Asp Gly Gln Leu Asp Phe Ser Glu Phe  
 5 65                      70                      75                      80  
 Leu Asn Leu Ile Gly Gly Leu Ala Met Ala Cys His Asp Ser Phe Leu  
 85                      90                      95  
 Lys Ala Val Pro Ser Gln Lys Arg Thr  
 100                      105

10

<210> 97

<211> 283

<212> PRT

15 <213> Homo sapiens

<400> 97

Met Val Asn Tyr Ala Trp Ala Gly Arg Ser Gln Arg Lys Leu Trp Trp  
 1                      5                      10                      15  
 20 Arg Ser Val Ala Val Leu Thr Cys Lys Ser Val Val Arg Pro Gly Tyr  
 20                      25                      30  
 Arg Gly Gly Leu Gln Ala Arg Arg Ser Thr Leu Leu Lys Thr Cys Ala  
 35                      40                      45  
 Arg Ala Arg Ala Thr Ala Pro Gly Ala Met Lys Met Val Ala Pro Trp  
 25 50                      55                      60  
 Thr Arg Phe Tyr Ser Asn Ser Cys Cys Leu Cys Cys His Val Arg Thr  
 65                      70                      75                      80  
 Gly Thr Ile Leu Leu Gly Val Trp Tyr Leu Ile Ile Asn Ala Val Val  
 85                      90                      95  
 329

Leu Leu Ile Leu Leu Ser Ala Leu Ala Asp Pro Asp Gln Tyr Asn Phe  
 100 105 110  
 Ser Ser Ser Glu Leu Gly Gly Asp Phe Glu Phe Met Asp Asp Ala Asn  
 115 120 125  
 5 Met Cys Ile Ala Ile Ala Ile Ser Leu Leu Met Ile Leu Ile Cys Ala  
 130 135 140  
 Met Ala Thr Tyr Gly Ala Tyr Lys Gln Arg Ala Ala Trp Ile Ile Pro  
 145 150 155 160  
 Phe Phe Cys Tyr Gln Ile Phe Asp Phe Ala Leu Asn Met Leu Val Ala  
 10 165 170 175  
 Ile Thr Val Leu Ile Tyr Pro Asn Ser Ile Gln Glu Tyr Ile Arg Gln  
 180 185 190  
 Leu Pro Pro Asn Phe Pro Tyr Arg Asp Asp Val Met Ser Val Asn Pro  
 195 200 205  
 15 Thr Cys Leu Val Leu Ile Ile Leu Leu Phe Ile Ser Ile Ile Leu Thr  
 210 215 220  
 Phe Lys Gly Tyr Leu Ile Ser Cys Val Trp Asn Cys Tyr Arg Tyr Ile  
 225 230 235 240  
 Asn Gly Arg Asn Ser Ser Asp Val Leu Val Tyr Val Thr Ser Asn Asp  
 20 245 250 255  
 Thr Thr Val Leu Leu Pro Pro Tyr Asp Asp Ala Thr Val Asn Gly Ala  
 260 265 270  
 Ala Lys Glu Pro Pro Pro Pro Tyr Val Ser Ala  
 275 280

25

<210> 98

<211> 712

<212> PRT

<213> Homo sapiens

<400> 98

Met Ala Gly Gly Pro Gly Pro Gly Glu Pro Ala Ala Pro Gly Ala Gln  
5 1 5 10 15  
His Phe Leu Tyr Glu Val Pro Pro Trp Val Met Cys Arg Phe Tyr Lys  
20 25 30  
Val Met Asp Ala Leu Glu Pro Ala Asp Trp Cys Gln Phe Ala Ala Leu  
35 40 45  
10 Ile Val Arg Asp Gln Thr Glu Leu Arg Leu Cys Glu Arg Ser Gly Gln  
50 55 60  
Arg Thr Ala Ser Val Leu Trp Pro Trp Ile Asn Arg Asn Ala Arg Val  
65 70 75 80  
Ala Asp Leu Val His Ile Leu Thr His Leu Gln Leu Leu Arg Ala Arg  
15 85 90 95  
Asp Ile Ile Thr Ala Trp His Pro Pro Ala Pro Leu Pro Ser Pro Gly  
100 105 110  
Thr Thr Ala Pro Arg Pro Ser Ser Ile Pro Ala Pro Ala Glu Ala Glu  
115 120 125  
20 Ala Trp Ser Pro Arg Lys Leu Pro Ser Ser Ala Ser Thr Phe Leu Ser  
130 135 140  
Pro Ala Phe Pro Gly Ser Gln Thr His Ser Gly Pro Glu Leu Gly Leu  
145 150 155 160  
Val Pro Ser Pro Ala Ser Leu Trp Pro Pro Pro Pro Ser Pro Ala Pro  
25 165 170 175  
Ser Ser Thr Lys Pro Gly Pro Glu Ser Ser Val Ser Leu Leu Gln Gly  
180 185 190  
Ala Arg Pro Ser Pro Phe Cys Trp Pro Leu Cys Glu Ile Ser Arg Gly  
195 200 205



Thr His Asn Phe Ser Glu Glu Leu Lys Ile Gly Glu Gly Gly Phe Gly  
 210 215 220  
 Cys Val Tyr Arg Ala Val Met Arg Asn Thr Val Tyr Ala Val Lys Arg  
 225 230 235 240  
 5 Leu Lys Glu Asn Ala Asp Leu Glu Trp Thr Ala Val Lys Gln Ser Phe  
 245 250 255  
 Leu Thr Glu Val Glu Gln Leu Ser Arg Phe Arg His Pro Asn Ile Val  
 260 265 270  
 Asp Phe Ala Gly Tyr Cys Ala Gln Asn Gly Phe Tyr Cys Leu Val Tyr  
 10 275 280 285  
 Gly Phe Leu Pro Asn Gly Ser Leu Glu Asp Arg Leu His Cys Gln Thr  
 290 295 300  
 Gln Ala Cys Pro Pro Leu Ser Trp Pro Gln Arg Leu Asp Ile Leu Leu  
 305 310 315 320  
 15 Gly Thr Ala Arg Ala Ile Gln Phe Leu His Gln Asp Ser Pro Ser Leu  
 325 330 335  
 Ile His Gly Asp Ile Lys Ser Ser Asn Val Leu Leu Asp Glu Arg Leu  
 340 345 350  
 Thr Pro Lys Leu Gly Asp Phe Gly Leu Ala Arg Phe Ser Arg Phe Ala  
 20 355 360 365  
 Gly Ser Ser Pro Ser Gln Ser Ser Met Val Ala Arg Thr Gln Thr Val  
 370 375 380  
 Arg Gly Thr Leu Ala Tyr Leu Pro Glu Glu Tyr Ile Lys Thr Gly Arg  
 385 390 395 400  
 25 Leu Ala Val Asp Thr Asp Thr Phe Ser Phe Gly Val Val Val Leu Glu  
 405 410 415  
 Thr Leu Ala Gly Gln Arg Ala Val Lys Thr His Gly Ala Arg Thr Lys  
 420 425 430  
 Tyr Leu Lys Asp Leu Val Glu Glu Glu Ala Glu Glu Ala Gly Val Ala  
 332

	435	440	445
	Leu Arg Ser Thr Gln Ser Thr Leu Gln Ala Gly Leu Ala Ala Asp Ala		
	450	455	460
	Trp Ala Ala Pro Ile Ala Met Gln Ile Tyr Lys Lys His Leu Asp Pro		
5	465	470	475 480
	Arg Pro Gly Pro Cys Pro Pro Glu Leu Gly Leu Gly Leu Gly Gln Leu		
	485	490	495
	Ala Cys Cys Cys Leu His Arg Arg Ala Lys Arg Arg Pro Pro Met Thr		
	500	505	510
10	Gln Val Tyr Glu Arg Leu Glu Lys Leu Gln Ala Val Val Ala Gly Val		
	515	520	525
	Pro Gly His Leu Glu Ala Ala Ser Cys Ile Pro Pro Ser Pro Gln Glu		
	530	535	540
	Asn Ser Tyr Val Ser Ser Thr Gly Arg Ala His Ser Gly Ala Ala Pro		
15	545	550	555 560
	Trp Gln Pro Leu Ala Ala Pro Ser Gly Ala Ser Ala Gln Ala Ala Glu		
	565	570	575
	Gln Leu Gln Arg Gly Pro Asn Gln Pro Val Glu Ser Asp Glu Ser Leu		
	580	585	590
20	Gly Gly Leu Ser Ala Ala Leu Arg Ser Trp His Leu Thr Pro Ser Cys		
	595	600	605
	Pro Leu Asp Pro Ala Pro Leu Arg Glu Ala Gly Cys Pro Gln Gly Asp		
	610	615	620
	Thr Ala Gly Glu Ser Ser Trp Gly Ser Gly Pro Gly Ser Arg Pro Thr		
25	625	630	635 640
	Ala Val Glu Gly Leu Ala Leu Gly Ser Ser Ala Ser Ser Ser Ser Glu		
	645	650	655
	Pro Pro Gln Ile Ile Ile Asn Pro Ala Arg Gln Lys Met Val Gln Lys		
	660	665	670
		333	

Leu Ala Leu Tyr Glu Asp Gly Ala Leu Asp Ser Leu Gln Leu Leu Ser  
675 680 685

Ser Ser Ser Leu Pro Gly Leu Gly Leu Glu Gln Asp Arg Gln Gly Pro  
690 695 700

5 Glu Glu Ser Asp Glu Phe Gln Ser  
705 710

<210> 99

10 <211> 132

<212> PRT

<213> Homo sapiens

<400> 99

15 Met Asn His Ile Val Gln Thr Phe Ser Pro Val Asn Ser Gly Gln Pro  
1 5 10 15

Pro Asn Tyr Glu Met Leu Lys Glu Glu Gln Glu Val Ala Met Leu Gly  
20 25 30

Gly Pro His Asn Pro Ala Pro Pro Thr Ser Thr Val Ile His Ile Arg  
20 35 40 45

Ser Glu Thr Ser Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr  
50 55 60

Leu Phe Met Asn Thr Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser  
65 70 75 80

25 Val Lys Ser Arg Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln  
85 90 95

Ala Tyr Ala Ser Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu  
100 105 110

Gly Ile Phe Met Thr Ile Leu Leu Val Ile Ile Pro Val Leu Val Val  
334

115                      120                      125  
 Gln Ala Gln Arg  
 130  
 5  
 <210> 100  
 <211> 207  
 <212> PRT  
 <213> Homo sapiens  
 10  
 <400> 100  
 Met Ala Pro Phe Glu Pro Leu Ala Ser Gly Ile Leu Leu Leu Leu Trp  
 1                      5                      10                      15  
 Leu Ile Ala Pro Ser Arg Ala Cys Thr Cys Val Pro Pro His Pro Gln  
 15                      20                      25                      30  
 Thr Ala Phe Cys Asn Ser Asp Leu Val Ile Arg Ala Lys Phe Val Gly  
 35                      40                      45  
 Thr Pro Glu Val Asn Gln Thr Thr Leu Tyr Gln Arg Tyr Glu Ile Lys  
 50                      55                      60  
 20 Met Thr Lys Met Tyr Lys Gly Phe Gln Ala Leu Gly Asp Ala Ala Asp  
 65                      70                      75                      80  
 Ile Arg Phe Val Tyr Thr Pro Ala Met Glu Ser Val Cys Gly Tyr Phe  
 85                      90                      95  
 His Arg Ser His Asn Arg Ser Glu Glu Phe Leu Ile Ala Gly Lys Leu  
 25                      100                      105                      110  
 Gln Asp Gly Leu Leu His Ile Thr Thr Cys Ser Phe Val Ala Pro Trp  
 115                      120                      125  
 Asn Ser Leu Ser Leu Ala Gln Arg Arg Gly Phe Thr Lys Thr Tyr Thr  
 130                      135                      140  
 335

Val Gly Cys Glu Glu Cys Thr Val Phe Pro Cys Leu Ser Ile Pro Cys  
 145                      150                      155                      160  
 Lys Leu Gln Ser Gly Thr His Cys Leu Trp Thr Asp Gln Leu Leu Gln  
                     165                      170                      175  
 5 Gly Ser Glu Lys Gly Phe Gln Ser Arg His Leu Ala Cys Leu Pro Arg  
                     180                      185                      190  
 Glu Pro Gly Leu Cys Thr Trp Gln Ser Leu Arg Ser Gln Ile Ala  
                     195                      200                      205  
  
 10  
 <210> 101  
 <211> 282  
 <212> PRT  
 <213> Homo sapiens  
  
 15  
 <400> 101  
 Met Glu Arg Pro Ser Leu Arg Ala Leu Leu Leu Gly Ala Ala Gly Leu  
 1                      5                      10                      15  
 Leu Leu Leu Leu Leu Pro Leu Ser Ser Ser Ser Ser Ser Asp Thr Cys  
 20                      20                      25                      30  
 Gly Pro Cys Glu Pro Ala Ser Cys Pro Pro Leu Pro Pro Leu Gly Cys  
                     35                      40                      45  
 Leu Leu Gly Glu Thr Arg Asp Ala Cys Gly Cys Cys Pro Met Cys Ala  
                     50                      55                      60  
 25 Arg Gly Glu Gly Glu Pro Cys Gly Gly Gly Gly Ala Gly Arg Gly Tyr  
                     65                      70                      75                      80  
 Cys Ala Pro Gly Met Glu Cys Val Lys Ser Arg Lys Arg Arg Lys Gly  
                     85                      90                      95  
 Lys Ala Gly Ala Ala Ala Gly Gly Pro Gly Val Ser Gly Val Cys Val  
                     336

	100	105	110
	Cys Lys Ser Arg Tyr Pro Val Cys Gly Ser Asp Gly Thr Thr Tyr Pro		
	115	120	125
	Ser Gly Cys Gln Leu Arg Ala Ala Ser Gln Arg Ala Glu Ser Arg Gly		
5	130	135	140
	Glu Lys Ala Ile Thr Gln Val Ser Lys Gly Thr Cys Glu Gln Gly Pro		
	145	150	155
	Ser Ile Val Thr Pro Pro Lys Asp Ile Trp Asn Val Thr Gly Ala Gln		
	165	170	175
10	Val Tyr Leu Ser Cys Glu Val Ile Gly Ile Pro Thr Pro Val Leu Ile		
	180	185	190
	Trp Asn Lys Val Lys Arg Gly His Tyr Gly Val Gln Arg Thr Glu Leu		
	195	200	205
	Leu Pro Gly Asp Arg Asp Asn Leu Ala Ile Gln Thr Arg Gly Gly Pro		
15	210	215	220
	Glu Lys His Glu Val Thr Gly Trp Val Leu Val Ser Pro Leu Ser Lys		
	225	230	235
	Glu Asp Ala Gly Glu Tyr Glu Cys His Ala Ser Asn Ser Gln Gly Gln		
	245	250	255
20	Ala Ser Ala Ser Ala Lys Ile Thr Val Val Asp Ala Leu His Glu Ile		
	260	265	270
	Pro Val Lys Lys Gly Glu Gly Ala Glu Leu		
	275	280	

25

<210> 102

<211> 125

<212> PRT

<213> Homo sapiens

<400> 102

Met His Lys Glu Glu His Glu Val Ala Val Leu Gly Ala Pro Pro Ser  
1 5 10 15  
5 Thr Ile Leu Pro Arg Ser Thr Val Ile Asn Ile His Ser Glu Thr Ser  
20 25 30  
Val Pro Asp His Val Val Trp Ser Leu Phe Asn Thr Leu Phe Leu Asn  
35 40 45  
Trp Cys Cys Leu Gly Phe Ile Ala Phe Ala Tyr Ser Val Lys Ser Arg  
10 50 55 60  
Asp Arg Lys Met Val Gly Asp Val Thr Gly Ala Gln Ala Tyr Ala Ser  
65 70 75 80  
Thr Ala Lys Cys Leu Asn Ile Trp Ala Leu Ile Leu Gly Ile Leu Met  
85 90 95  
15 Thr Ile Gly Phe Ile Leu Leu Leu Val Phe Gly Ser Val Thr Val Tyr  
100 105 110  
His Ile Met Leu Gln Ile Ile Gln Glu Lys Arg Gly Tyr  
115 120 125

20

<210> 103

<211> 1466

<212> PRT

<213> Homo sapiens

25

<400> 103

Met Met Ser Phe Val Gln Lys Gly Ser Trp Leu Leu Leu Ala Leu Leu  
1 5 10 15  
His Pro Thr Ile Ile Leu Ala Gln Gln Glu Ala Val Glu Gly Gly Cys  
338

	20	25	30
	Ser His Leu Gly Gln Ser Tyr Ala Asp Arg Asp Val Trp Lys Pro Glu		
	35	40	45
	Pro Cys Gln Ile Cys Val Cys Asp Ser Gly Ser Val Leu Cys Asp Asp		
5	50	55	60
	Ile Ile Cys Asp Asp Gln Glu Leu Asp Cys Pro Asn Pro Glu Ile Pro		
	65	70	75 80
	Phe Gly Glu Cys Cys Ala Val Cys Pro Gln Pro Pro Thr Ala Pro Thr		
	85	90	95
10	Arg Pro Pro Asn Gly Gln Gly Pro Gln Gly Pro Lys Gly Asp Pro Gly		
	100	105	110
	Pro Pro Gly Ile Pro Gly Arg Asn Gly Asp Pro Gly Ile Pro Gly Gln		
	115	120	125
	Pro Gly Ser Pro Gly Ser Pro Gly Pro Pro Gly Ile Cys Glu Ser Cys		
15	130	135	140
	Pro Thr Gly Pro Gln Asn Tyr Ser Pro Gln Tyr Asp Ser Tyr Asp Val		
	145	150	155 160
	Lys Ser Gly Val Ala Val Gly Gly Leu Ala Gly Tyr Pro Gly Pro Ala		
	165	170	175
20	Gly Pro Pro Gly Pro Pro Gly Pro Pro Gly Thr Ser Gly His Pro Gly		
	180	185	190
	Ser Pro Gly Ser Pro Gly Tyr Gln Gly Pro Pro Gly Glu Pro Gly Gln		
	195	200	205
	Ala Gly Pro Ser Gly Pro Pro Gly Pro Pro Gly Ala Ile Gly Pro Ser		
25	210	215	220
	Gly Pro Ala Gly Lys Asp Gly Glu Ser Gly Arg Pro Gly Arg Pro Gly		
	225	230	235 240
	Glu Arg Gly Leu Pro Gly Pro Pro Gly Ile Lys Gly Pro Ala Gly Ile		
	245	250	255
	339		



Pro Gly Phe Pro Gly Met Lys Gly His Arg Gly Phe Asp Gly Arg Asn  
 260 265 270  
 Gly Glu Lys Gly Glu Thr Gly Ala Pro Gly Leu Lys Gly Glu Asn Gly  
 275 280 285  
 5 Leu Pro Gly Glu Asn Gly Ala Pro Gly Pro Met Gly Pro Arg Gly Ala  
 290 295 300  
 Pro Gly Glu Arg Gly Arg Pro Gly Leu Pro Gly Ala Ala Gly Ala Arg  
 305 310 315 320  
 Gly Asn Asp Gly Ala Arg Gly Ser Asp Gly Gln Pro Gly Pro Pro Gly  
 10 325 330 335  
 Pro Pro Gly Thr Ala Gly Phe Pro Gly Ser Pro Gly Ala Lys Gly Glu  
 340 345 350  
 Val Gly Pro Ala Gly Ser Pro Gly Ser Asn Gly Ala Pro Gly Gln Arg  
 355 360 365  
 15 Gly Glu Pro Gly Pro Gln Gly His Ala Gly Ala Gln Gly Pro Pro Gly  
 370 375 380  
 Pro Pro Gly Ile Asn Gly Ser Pro Gly Gly Lys Gly Glu Met Gly Pro  
 385 390 395 400  
 Ala Gly Ile Pro Gly Ala Pro Gly Leu Met Gly Ala Arg Gly Pro Pro  
 20 405 410 415  
 Gly Pro Ala Gly Ala Asn Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly  
 420 425 430  
 Glu Pro Gly Lys Asn Gly Ala Lys Gly Glu Pro Gly Pro Arg Gly Glu  
 435 440 445  
 25 Arg Gly Glu Ala Gly Ile Pro Gly Val Pro Gly Ala Lys Gly Glu Asp  
 450 455 460  
 Gly Lys Asp Gly Ser Pro Gly Glu Pro Gly Ala Asn Gly Leu Pro Gly  
 465 470 475 480  
 Ala Ala Gly Glu Arg Gly Ala Pro Gly Phe Arg Gly Pro Ala Gly Pro  
 340

	485	490	495
	Asn Gly Ile Pro Gly Glu Lys Gly Pro Ala Gly Glu Arg Gly Ala Pro		
	500	505	510
	Gly Pro Ala Gly Pro Arg Gly Ala Ala Gly Glu Pro Gly Arg Asp Gly		
5	515	520	525
	Val Pro Gly Gly Pro Gly Met Arg Gly Met Pro Gly Ser Pro Gly Gly		
	530	535	540
	Pro Gly Ser Asp Gly Lys Pro Gly Pro Pro Gly Ser Gln Gly Glu Ser		
	545	550	555
			560
10	Gly Arg Pro Gly Pro Pro Gly Pro Ser Gly Pro Arg Gly Gln Pro Gly		
	565	570	575
	Val Met Gly Phe Pro Gly Pro Lys Gly Asn Asp Gly Ala Pro Gly Lys		
	580	585	590
	Asn Gly Glu Arg Gly Gly Pro Gly Gly Pro Gly Pro Gln Gly Pro Pro		
15	595	600	605
	Gly Lys Asn Gly Glu Thr Gly Pro Gln Gly Pro Pro Gly Pro Thr Gly		
	610	615	620
	Pro Gly Gly Asp Lys Gly Asp Thr Gly Pro Pro Gly Pro Gln Gly Leu		
	625	630	635
			640
20	Gln Gly Leu Pro Gly Thr Gly Gly Pro Pro Gly Glu Asn Gly Lys Pro		
	645	650	655
	Gly Glu Pro Gly Pro Lys Gly Asp Ala Gly Ala Pro Gly Ala Pro Gly		
	660	665	670
	Gly Lys Gly Asp Ala Gly Ala Pro Gly Glu Arg Gly Pro Pro Gly Leu		
25	675	680	685
	Ala Gly Ala Pro Gly Leu Arg Gly Gly Ala Gly Pro Pro Gly Pro Glu		
	690	695	700
	Gly Gly Lys Gly Ala Ala Gly Pro Pro Gly Pro Pro Gly Ala Ala Gly		
	705	710	715
			720

Thr Pro Gly Leu Gln Gly Met Pro Gly Glu Arg Gly Gly Leu Gly Ser  
 725 730 735  
 Pro Gly Pro Lys Gly Asp Lys Gly Glu Pro Gly Gly Pro Gly Ala Asp  
 740 745 750  
 5 Gly Val Pro Gly Lys Asp Gly Pro Arg Gly Pro Thr Gly Pro Ile Gly  
 755 760 765  
 Pro Pro Gly Pro Ala Gly Gln Pro Gly Asp Lys Gly Glu Gly Gly Ala  
 770 775 780  
 Pro Gly Leu Pro Gly Ile Ala Gly Pro Arg Gly Ser Pro Gly Glu Arg  
 10 785 790 795 800  
 Gly Glu Thr Gly Pro Pro Gly Pro Ala Gly Phe Pro Gly Ala Pro Gly  
 805 810 815  
 Gln Asn Gly Glu Pro Gly Gly Lys Gly Glu Arg Gly Ala Pro Gly Glu  
 820 825 830  
 15 Lys Gly Glu Gly Gly Pro Pro Gly Val Ala Gly Pro Pro Gly Gly Ser  
 835 840 845  
 Gly Pro Ala Gly Pro Pro Gly Pro Gln Gly Val Lys Gly Glu Arg Gly  
 850 855 860  
 Ser Pro Gly Gly Pro Gly Ala Ala Gly Phe Pro Gly Ala Arg Gly Leu  
 20 865 870 875 880  
 Pro Gly Pro Pro Gly Ser Asn Gly Asn Pro Gly Pro Pro Gly Pro Ser  
 885 890 895  
 Gly Ser Pro Gly Lys Asp Gly Pro Pro Gly Pro Ala Gly Asn Thr Gly  
 900 905 910  
 25 Ala Pro Gly Ser Pro Gly Val Ser Gly Pro Lys Gly Asp Ala Gly Gln  
 915 920 925  
 Pro Gly Glu Lys Gly Ser Pro Gly Ala Gln Gly Pro Pro Gly Ala Pro  
 930 935 940  
 Gly Pro Leu Gly Ile Ala Gly Ile Thr Gly Ala Arg Gly Leu Ala Gly

	945	950	955	960
	Pro	Pro	Gly	Met
	Pro	Gly	Pro	Arg
	Gly	Ser	Pro	Gly
	Pro	Gln	Gly	Val
	965	970	975	
	Lys	Gly	Glu	Ser
	Gly	Lys	Pro	Gly
	Ala	Asn	Gly	Leu
	Ser	Gly	Glu	Arg
5	980	985	990	
	Gly	Pro	Pro	Gly
	Pro	Gln	Gly	Leu
	Pro	Gly	Leu	Ala
	Gly	Thr	Ala	Gly
	995	1000	1005	
	Glu	Pro	Gly	Arg
	Asp	Gly	Asn	Pro
	Gly	Ser	Asp	Gly
	Leu	Pro	Gly	Arg
	1010	1015	1020	
10	Asp	Gly	Ser	Pro
	Gly	Gly	Lys	Gly
	Asp	Arg	Gly	Glu
	Asn	Gly	Ser	Pro
	1025	1030	1035	1040
	Gly	Ala	Pro	Gly
	Ala	Pro	Gly	His
	Pro	Gly	Pro	Pro
	Gly	Pro	Val	Gly
	1045	1050	1055	
	Pro	Ala	Gly	Lys
	Ser	Gly	Asp	Arg
	Gly	Glu	Ser	Gly
	Pro	Ala	Gly	Pro
15	1060	1065	1070	
	Ala	Gly	Ala	Pro
	Gly	Pro	Ala	Gly
	Ser	Arg	Gly	Ala
	Pro	Gly	Pro	Gln
	1075	1080	1085	
	Gly	Pro	Arg	Gly
	Asp	Lys	Gly	Glu
	Thr	Gly	Glu	Arg
	Gly	Ala	Ala	Gly
	1090	1095	1100	
20	Ile	Lys	Gly	His
	Arg	Gly	Phe	Pro
	Gly	Asn	Pro	Gly
	Ala	Pro	Gly	Ser
	1105	1110	1115	1120
	Pro	Gly	Pro	Ala
	Gly	Gln	Gln	Gly
	Ala	Ile	Gly	Ser
	Pro	Gly	Pro	Ala
	1125	1130	1135	
	Gly	Pro	Arg	Gly
	Pro	Val	Gly	Pro
	Ser	Gly	Pro	Pro
	Gly	Lys	Asp	Gly
25	1140	1145	1150	
	Thr	Ser	Gly	His
	Pro	Gly	Pro	Ile
	Gly	Pro	Pro	Gly
	Pro	Arg	Gly	Asn
	1155	1160	1165	
	Arg	Gly	Glu	Arg
	Gly	Ser	Glu	Gly
	Ser	Pro	Gly	His
	Pro	Gly	Gln	Pro
	1170	1175	1180	

Gly Pro Pro Gly Pro Pro Gly Ala Pro Gly Pro Cys Cys Gly Gly Val  
 1185 1190 1195 1200  
 Gly Ala Ala Ala Ile Ala Gly Ile Gly Gly Glu Lys Ala Gly Gly Phe  
 1205 1210 1215  
 5 Ala Pro Tyr Tyr Gly Asp Glu Pro Met Asp Phe Lys Ile Asn Thr Asp  
 1220 1225 1230  
 Glu Ile Met Thr Ser Leu Lys Ser Val Asn Gly Gln Ile Glu Ser Leu  
 1235 1240 1245  
 Ile Ser Pro Asp Gly Ser Arg Lys Asn Pro Ala Arg Asn Cys Arg Asp  
 10 1250 1255 1260  
 Leu Lys Phe Cys His Pro Glu Leu Lys Ser Gly Glu Tyr Trp Val Asp  
 1265 1270 1275 1280  
 Pro Asn Gln Gly Cys Lys Leu Asp Ala Ile Lys Val Phe Cys Asn Met  
 1285 1290 1295  
 15 Glu Thr Gly Glu Thr Cys Ile Ser Ala Asn Pro Leu Asn Val Pro Arg  
 1300 1305 1310  
 Lys His Trp Trp Thr Asp Ser Ser Ala Glu Lys Lys His Val Trp Phe  
 1315 1320 1325  
 Gly Glu Ser Met Asp Gly Gly Phe Gln Phe Ser Tyr Gly Asn Pro Glu  
 20 1330 1335 1340  
 Leu Pro Glu Asp Val Leu Asp Val Gln Leu Ala Phe Leu Arg Leu Leu  
 1345 1350 1355 1360  
 Ser Ser Arg Ala Ser Gln Asn Ile Thr Tyr His Cys Lys Asn Ser Ile  
 1365 1370 1375  
 25 Ala Tyr Met Asp Gln Ala Ser Gly Asn Val Lys Lys Ala Leu Lys Leu  
 1380 1385 1390  
 Met Gly Ser Asn Glu Gly Glu Phe Lys Ala Glu Gly Asn Ser Lys Phe  
 1395 1400 1405  
 Thr Tyr Thr Val Leu Glu Asp Gly Cys Thr Lys His Thr Gly Glu Trp

1410                      1415                      1420  
 Ser Lys Thr Val Phe Glu Tyr Arg Thr Arg Lys Ala Val Arg Leu Pro  
 1425                      1430                      1435                      1440  
 Ile Val Asp Ile Ala Pro Tyr Asp Ile Gly Gly Pro Asp Gln Glu Phe  
 5                      1445                      1450                      1455  
 Gly Val Asp Val Gly Pro Val Cys Phe Leu  
                     1460                      1465

10 <210> 104  
     <211> 272  
     <212> PRT  
     <213> Homo sapiens

15 <400> 104  
 Met Val Leu Leu Thr Ala Val Leu Leu Leu Leu Ala Ala Tyr Ala Gly  
     1                      5                      10                      15  
 Pro Ala Gln Ser Leu Gly Ser Phe Val His Cys Glu Pro Cys Asp Glu  
                     20                      25                      30  
 20 Lys Ala Leu Ser Met Cys Pro Pro Ser Pro Leu Gly Cys Glu Leu Val  
                     35                      40                      45  
 Lys Glu Pro Gly Cys Gly Cys Cys Met Thr Cys Ala Leu Ala Glu Gly  
                     50                      55                      60  
 Gln Ser Cys Gly Val Tyr Thr Glu Arg Cys Ala Gln Gly Leu Arg Cys  
 25 65                      70                      75                      80  
 Leu Pro Arg Gln Asp Glu Glu Lys Pro Leu His Ala Leu Leu His Gly  
                     85                      90                      95  
 Arg Gly Val Cys Leu Asn Glu Lys Ser Tyr Arg Glu Gln Val Lys Ile  
                     100                      105                      110  
     345

Glu Arg Asp Ser Arg Glu His Glu Glu Pro Thr Thr Ser Glu Met Ala  
 115 120 125  
 Glu Glu Thr Tyr Ser Pro Lys Ile Phe Arg Pro Lys His Thr Arg Ile  
 130 135 140  
 5 Ser Glu Leu Lys Ala Glu Ala Val Lys Lys Asp Arg Arg Lys Lys Leu  
 145 150 155 160  
 Thr Gln Ser Lys Phe Val Gly Gly Ala Glu Asn Thr Ala His Pro Arg  
 165 170 175  
 Ile Ile Ser Ala Pro Glu Met Arg Gln Glu Ser Glu Gln Gly Pro Cys  
 10 180 185 190  
 Arg Arg His Met Glu Ala Ser Leu Gln Glu Leu Lys Ala Ser Pro Arg  
 195 200 205  
 Met Val Pro Arg Ala Val Tyr Leu Pro Asn Cys Asp Arg Lys Gly Phe  
 210 215 220  
 15 Tyr Lys Arg Lys Gln Cys Lys Pro Ser Arg Gly Arg Lys Arg Gly Ile  
 225 230 235 240  
 Cys Trp Cys Val Asp Lys Tyr Gly Met Lys Leu Pro Gly Met Glu Tyr  
 245 250 255  
 Val Asp Gly Asp Phe Gln Cys His Thr Phe Asp Ser Ser Asn Val Glu  
 20 260 265 270

<210> 105

<211> 158

25 <212> PRT

<213> Homo sapiens

<400> 105

Met Ala Ser Arg Ser Met Arg Leu Leu Leu Leu Ser Cys Leu Ala

1                      5                      10                      15  
 Lys Thr Gly Val Leu Gly Asp Ile Ile Met Arg Pro Ser Cys Ala Pro  
                     20                      25                      30  
 Gly Trp Phe Tyr His Lys Ser Asn Cys Tyr Gly Tyr Phe Arg Lys Leu  
 5                      35                      40                      45  
 Arg Asn Trp Ser Asp Ala Glu Leu Glu Cys Gln Ser Tyr Gly Asn Gly  
                     50                      55                      60  
 Ala His Leu Ala Ser Ile Leu Ser Leu Lys Glu Ala Ser Thr Ile Ala  
 65                      70                      75                      80  
 10 Glu Tyr Ile Ser Gly Tyr Gln Arg Ser Gln Pro Ile Trp Ile Gly Leu  
                     85                      90                      95  
 His Asp Pro Gln Lys Arg Gln Gln Trp Gln Trp Ile Asp Gly Ala Met  
                     100                      105                      110  
 Tyr Leu Tyr Arg Ser Trp Ser Gly Lys Ser Met Gly Gly Asn Lys His  
 15                      115                      120                      125  
 Cys Ala Glu Met Ser Ser Asn Asn Asn Phe Leu Thr Trp Ser Ser Asn  
                     130                      135                      140  
 Glu Cys Asn Lys Arg Gln His Phe Leu Cys Lys Tyr Arg Pro  
 145                      150                      155  
 20

<210> 106

<211> 175

<212> PRT

25 <213> Homo sapiens

<400> 106

Met Glu Lys Ile Pro Val Ser Ala Phe Leu Leu Leu Val Ala Leu Ser

1                      5                      10                      15



Tyr Thr Leu Ala Arg Asp Thr Thr Val Lys Pro Gly Ala Lys Lys Asp  
 20 25 30  
 Thr Lys Asp Ser Arg Pro Lys Leu Pro Gln Thr Leu Ser Arg Gly Trp  
 35 40 45  
 5 Gly Asp Gln Leu Ile Trp Thr Gln Thr Tyr Glu Glu Ala Leu Tyr Lys  
 50 55 60  
 Ser Lys Thr Ser Asn Lys Pro Leu Met Ile Ile His His Leu Asp Glu  
 65 70 75 80  
 Cys Pro His Ser Gln Ala Leu Lys Lys Val Phe Ala Glu Asn Lys Glu  
 10 85 90 95  
 Ile Gln Lys Leu Ala Glu Gln Phe Val Leu Leu Asn Leu Val Tyr Glu  
 100 105 110  
 Thr Thr Asp Lys His Leu Ser Pro Asp Gly Gln Tyr Val Pro Arg Ile  
 115 120 125  
 15 Met Phe Val Asp Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg  
 130 135 140  
 Tyr Ser Asn Arg Leu Tyr Ala Tyr Glu Pro Ala Asp Thr Ala Leu Leu  
 145 150 155 160  
 Leu Asp Asn Met Lys Lys Ala Leu Lys Leu Leu Lys Thr Glu Leu  
 20 165 170 175

<210> 107

<211> 732

25 <212> PRT

<213> Homo sapiens

<400> 107

Met Pro Glu Glu Thr Gln Thr Gln Asp Gln Pro Met Glu Glu Glu Glu

	1	5	10	15
	Val Glu Thr Phe Ala Phe Gln Ala Glu Ile Ala Gln Leu Met Ser Leu			
	20	25	30	
	Ile Ile Asn Thr Phe Tyr Ser Asn Lys Glu Ile Phe Leu Arg Glu Leu			
5	35	40	45	
	Ile Ser Asn Ser Ser Asp Ala Leu Asp Lys Ile Arg Tyr Glu Ser Leu			
	50	55	60	
	Thr Asp Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu			
	65	70	75	80
10	Ile Pro Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Asp Thr Gly Ile			
	85	90	95	
	Gly Met Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Lys			
	100	105	110	
	Ser Gly Thr Lys Ala Phe Met Glu Ala Leu Gln Ala Gly Ala Asp Ile			
15	115	120	125	
	Ser Met Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val			
	130	135	140	
	Ala Glu Lys Val Thr Val Ile Thr Lys His Asn Asp Asp Glu Gln Tyr			
	145	150	155	160
20	Ala Trp Glu Ser Ser Ala Gly Gly Ser Phe Thr Val Arg Thr Asp Thr			
	165	170	175	
	Gly Glu Pro Met Gly Arg Gly Thr Lys Val Ile Leu His Leu Lys Glu			
	180	185	190	
	Asp Gln Thr Glu Tyr Leu Glu Glu Arg Arg Ile Lys Glu Ile Val Lys			
25	195	200	205	
	Lys His Ser Gln Phe Ile Gly Tyr Pro Ile Thr Leu Phe Val Glu Lys			
	210	215	220	
	Glu Arg Asp Lys Glu Val Ser Asp Asp Glu Ala Glu Glu Lys Glu Asp			
	225	230	235	240
	349			

[illegible]

	465	470	475	480
	Cys Thr Arg Met Lys Glu Asn Gln Lys His Ile Tyr Tyr Ile Thr Gly			
	485	490	495	
	Glu Thr Lys Asp Gln Val Ala Asn Ser Ala Phe Val Glu Arg Leu Arg			
5	500	505	510	
	Lys His Gly Leu Glu Val Ile Tyr Met Ile Glu Pro Ile Asp Glu Tyr			
	515	520	525	
	Cys Val Gln Gln Leu Lys Glu Phe Glu Gly Lys Thr Leu Val Ser Val			
	530	535	540	
10	Thr Lys Glu Gly Leu Glu Leu Pro Glu Asp Glu Glu Glu Lys Lys Lys			
	545	550	555	560
	Gln Glu Glu Lys Lys Thr Lys Phe Glu Asn Leu Cys Lys Ile Met Lys			
	565	570	575	
	Asp Ile Leu Glu Lys Lys Val Glu Lys Val Val Val Ser Asn Arg Leu			
15	580	585	590	
	Val Thr Ser Pro Cys Cys Ile Val Thr Ser Thr Tyr Gly Trp Thr Ala			
	595	600	605	
	Asn Met Glu Arg Ile Met Lys Ala Gln Ala Leu Arg Asp Asn Ser Thr			
	610	615	620	
20	Met Gly Tyr Met Ala Ala Lys Lys His Leu Glu Ile Asn Pro Asp His			
	625	630	635	640
	Ser Ile Ile Glu Thr Leu Arg Gln Lys Ala Glu Ala Asp Lys Asn Asp			
	645	650	655	
	Lys Ser Val Lys Asp Leu Val Ile Leu Leu Tyr Glu Thr Ala Leu Leu			
25	660	665	670	
	Ser Ser Gly Phe Ser Leu Glu Asp Pro Gln Thr His Ala Asn Arg Ile			
	675	680	685	
	Tyr Arg Met Ile Lys Leu Gly Leu Gly Ile Asp Glu Asp Asp Pro Thr			
	690	695	700	

Ala Asp Asp Thr Ser Ala Ala Val Thr Glu Glu Met Pro Pro Leu Glu  
705 710 715 720

Gly Asp Asp Asp Thr Ser Arg Met Glu Glu Val Asp  
725 730

5

<210> 108

<211> 1361

<212> PRT

10 <213> Homo sapiens

<400> 108

Met Gly Ala Ala Gly Arg Gln Asp Phe Leu Phe Lys Ala Met Leu Thr  
1 5 10 15

15 Ile Ser Trp Leu Thr Leu Thr Cys Phe Pro Gly Ala Thr Ser Thr Val  
20 25 30

Ala Ala Gly Cys Pro Asp Gln Ser Pro Glu Leu Gln Pro Trp Asn Pro  
35 40 45

Gly His Asp Gln Asp His His Val His Ile Gly Gln Gly Lys Thr Leu  
20 50 55 60

Leu Leu Thr Ser Ser Ala Thr Val Tyr Ser Ile His Ile Ser Glu Gly  
65 70 75 80

Gly Lys Leu Val Ile Lys Asp His Asp Glu Pro Ile Val Leu Arg Thr  
85 90 95

25 Arg His Ile Leu Ile Asp Asn Gly Gly Glu Leu His Ala Gly Ser Ala  
100 105 110

Leu Cys Pro Phe Gln Gly Asn Phe Thr Ile Ile Leu Tyr Gly Arg Ala  
115 120 125

Asp Glu Gly Ile Gln Pro Asp Pro Tyr Tyr Gly Leu Lys Tyr Ile Gly  
352

	130	135	140	
	Val Gly Lys Gly Gly Ala Leu Glu Leu His Gly Gln Lys Lys Leu Ser			
	145	150	155	160
	Trp Thr Phe Leu Asn Lys Thr Leu His Pro Gly Gly Met Ala Glu Gly			
5	165	170	175	
	Gly Tyr Phe Phe Glu Arg Ser Trp Gly His Arg Gly Val Ile Val His			
	180	185	190	
	Val Ile Asp Pro Lys Ser Gly Thr Val Ile His Ser Asp Arg Phe Asp			
	195	200	205	
10	Thr Tyr Arg Ser Lys Lys Glu Ser Glu Arg Leu Val Gln Tyr Leu Asn			
	210	215	220	
	Ala Val Pro Asp Gly Arg Ile Leu Ser Val Ala Val Asn Asp Glu Gly			
	225	230	235	240
	Ser Arg Asn Leu Asp Asp Met Ala Arg Lys Ala Met Thr Lys Leu Gly			
15	245	250	255	
	Ser Lys His Phe Leu His Leu Gly Phe Arg His Pro Trp Ser Phe Leu			
	260	265	270	
	Thr Val Lys Gly Asn Pro Ser Ser Ser Val Glu Asp His Ile Glu Tyr			
	275	280	285	
20	His Gly His Arg Gly Ser Ala Ala Ala Arg Val Phe Lys Leu Phe Gln			
	290	295	300	
	Thr Glu His Gly Glu Tyr Phe Asn Val Ser Leu Ser Ser Glu Trp Val			
	305	310	315	320
	Gln Asp Val Glu Trp Thr Glu Trp Phe Asp His Asp Lys Val Ser Gln			
25	325	330	335	
	Thr Lys Gly Gly Glu Lys Ile Ser Asp Leu Trp Lys Ala His Pro Gly			
	340	345	350	
	Lys Ile Cys Asn Arg Pro Ile Asp Ile Gln Ala Thr Thr Met Asp Gly			
	355	360	365	
		353		

Val Asn Leu Ser Thr Glu Val Val Tyr Lys Lys Gly Gln Asp Tyr Arg  
 370 375 380  
 Phe Ala Cys Tyr Asp Arg Gly Arg Ala Cys Arg Ser Tyr Arg Val Arg  
 385 390 395 400  
 5 Phe Leu Cys Gly Lys Pro Val Arg Pro Lys Leu Thr Val Thr Ile Asp  
 405 410 415  
 Thr Asn Val Asn Ser Thr Ile Leu Asn Leu Glu Asp Asn Val Gln Ser  
 420 425 430  
 Trp Lys Pro Gly Asp Thr Leu Val Ile Ala Ser Thr Asp Tyr Ser Met  
 10 435 440 445  
 Tyr Gln Ala Glu Glu Phe Gln Val Leu Pro Cys Arg Ser Cys Ala Pro  
 450 455 460  
 Asn Gln Val Lys Val Ala Gly Lys Pro Met Tyr Leu His Ile Gly Glu  
 465 470 475 480  
 15 Glu Ile Asp Gly Val Asp Met Arg Ala Glu Val Gly Leu Leu Ser Arg  
 485 490 495  
 Asn Ile Ile Val Met Gly Glu Met Glu Asp Lys Cys Tyr Pro Tyr Arg  
 500 505 510  
 Asn His Ile Cys Asn Phe Phe Asp Phe Asp Thr Phe Gly Gly His Ile  
 20 515 520 525  
 Lys Phe Ala Leu Gly Phe Lys Ala Ala His Leu Glu Gly Thr Glu Leu  
 530 535 540  
 Lys His Met Gly Gln Gln Leu Val Gly Gln Tyr Pro Ile His Phe His  
 545 550 555 560  
 25 Leu Ala Gly Asp Val Asp Glu Arg Gly Gly Tyr Asp Pro Pro Thr Tyr  
 565 570 575  
 Ile Arg Asp Leu Ser Ile His His Thr Phe Ser Arg Cys Val Thr Val  
 580 585 590  
 His Gly Ser Asn Gly Leu Leu Ile Lys Asp Val Val Gly Tyr Asn Ser  
 354

	595	600	605
	Leu Gly His Cys Phe Phe Thr Glu Asp Gly Pro Glu Glu Arg Asn Thr		
	610	615	620
	Phe Asp His Cys Leu Gly Leu Leu Val Lys Ser Gly Thr Leu Leu Pro		
5	625	630	635 640
	Ser Asp Arg Asp Ser Lys Met Cys Lys Met Ile Thr Glu Asp Ser Tyr		
	645	650	655
	Pro Gly Tyr Ile Pro Lys Pro Arg Gln Asp Cys Asn Ala Val Ser Thr		
	660	665	670
10	Phe Trp Met Ala Asn Pro Asn Asn Asn Leu Ile Asn Cys Ala Ala Ala		
	675	680	685
	Gly Ser Glu Glu Thr Gly Phe Trp Phe Ile Phe His His Val Pro Thr		
	690	695	700
	Gly Pro Ser Val Gly Met Tyr Ser Pro Gly Tyr Ser Glu His Ile Pro		
15	705	710	715 720
	Leu Gly Lys Phe Tyr Asn Asn Arg Ala His Ser Asn Tyr Arg Ala Gly		
	725	730	735
	Met Ile Ile Asp Asn Gly Val Lys Thr Thr Glu Ala Ser Ala Lys Asp		
	740	745	750
20	Lys Arg Pro Phe Leu Ser Ile Ile Ser Ala Arg Tyr Ser Pro His Gln		
	755	760	765
	Asp Ala Asp Pro Leu Lys Pro Arg Glu Pro Ala Ile Ile Arg His Phe		
	770	775	780
	Ile Ala Tyr Lys Asn Gln Asp His Gly Ala Trp Leu Arg Gly Gly Asp		
25	785	790	795 800
	Val Trp Leu Asp Ser Cys Arg Phe Ala Asp Asn Gly Ile Gly Leu Thr		
	805	810	815
	Leu Ala Ser Gly Gly Thr Phe Pro Tyr Asp Asp Gly Ser Lys Gln Glu		
	820	825	830
		355	



Ile Lys Asn Ser Leu Phe Val Gly Glu Ser Gly Asn Val Gly Thr Glu  
 835 840 845  
 Met Met Asp Asn Arg Ile Trp Gly Pro Gly Gly Leu Asp His Ser Gly  
 850 855 860  
 5 Arg Thr Leu Pro Ile Gly Gln Asn Phe Pro Ile Arg Gly Ile Gln Leu  
 865 870 875 880  
 Tyr Asp Gly Pro Ile Asn Ile Gln Asn Cys Thr Phe Arg Lys Phe Val  
 885 890 895  
 Ala Leu Glu Gly Arg His Thr Ser Ala Leu Ala Phe Arg Leu Asn Asn  
 10 900 905 910  
 Ala Trp Gln Ser Cys Pro His Asn Asn Val Thr Gly Ile Ala Phe Glu  
 915 920 925  
 Asp Val Pro Ile Thr Ser Arg Val Phe Phe Gly Glu Pro Gly Pro Trp  
 930 935 940  
 15 Phe Asn Gln Leu Asp Met Asp Gly Asp Lys Thr Ser Val Phe His Asp  
 945 950 955 960  
 Val Asp Gly Ser Val Ser Glu Tyr Pro Gly Ser Tyr Leu Thr Lys Asn  
 965 970 975  
 Asp Asn Trp Leu Val Arg His Pro Asp Cys Ile Asn Val Pro Asp Trp  
 20 980 985 990  
 Arg Gly Ala Ile Cys Ser Gly Cys Tyr Ala Gln Met Tyr Ile Gln Ala  
 995 1000 1005  
 Tyr Lys Thr Ser Asn Leu Arg Met Lys Ile Ile Lys Asn Asp Phe Pro  
 1010 1015 1020  
 25 Ser His Pro Leu Tyr Leu Glu Gly Ala Leu Thr Arg Ser Thr His Tyr  
 1025 1030 1035 1040  
 Gln Gln Tyr Gln Pro Val Val Thr Leu Gln Lys Gly Tyr Thr Ile His  
 1045 1050 1055  
 Trp Asp Gln Thr Ala Pro Ala Glu Leu Ala Ile Trp Leu Ile Asn Phe

	1060	1065	1070
	Asn Lys Gly Asp Trp Ile Arg Val Gly Leu Cys Tyr Pro Arg Gly Thr		
	1075	1080	1085
	Thr Phe Ser Ile Leu Ser Asp Val His Asn Arg Leu Leu Lys Gln Thr		
5	1090	1095	1100
	Ser Lys Thr Gly Val Phe Val Arg Thr Leu Gln Met Asp Lys Val Glu		
	1105	1110	1115 1120
	Gln Ser Tyr Pro Gly Arg Ser His Tyr Tyr Trp Asp Glu Asp Ser Gly		
	1125	1130	1135
10	Leu Leu Phe Leu Lys Leu Lys Ala Gln Asn Glu Arg Glu Lys Phe Ala		
	1140	1145	1150
	Phe Cys Ser Met Lys Gly Cys Glu Arg Ile Lys Ile Lys Ala Leu Ile		
	1155	1160	1165
	Pro Lys Asn Ala Gly Val Ser Asp Cys Thr Ala Thr Ala Tyr Pro Lys		
15	1170	1175	1180
	Phe Thr Glu Arg Ala Val Val Asp Val Pro Met Pro Lys Lys Leu Phe		
	1185	1190	1195 1200
	Gly Ser Gln Leu Lys Thr Lys Asp His Phe Leu Glu Val Lys Met Glu		
	1205	1210	1215
20	Ser Ser Lys Gln His Phe Phe His Leu Trp Asn Asp Phe Ala Tyr Ile		
	1220	1225	1230
	Glu Val Asp Gly Lys Lys Tyr Pro Ser Ser Glu Asp Gly Ile Gln Val		
	1235	1240	1245
	Val Val Ile Asp Gly Asn Gln Gly Arg Val Val Ser His Thr Ser Phe		
25	1250	1255	1260
	Arg Asn Ser Ile Leu Gln Gly Ile Pro Trp Gln Leu Phe Asn Tyr Val		
	1265	1270	1275 1280
	Ala Thr Ile Pro Asp Asn Ser Ile Val Leu Met Ala Ser Lys Gly Arg		
	1285	1290	1295

Tyr Val Ser Arg Gly Pro Trp Thr Arg Val Leu Glu Lys Leu Gly Ala

1300

1305

1310

Asp Arg Gly Leu Lys Leu Lys Glu Gln Met Ala Phe Val Gly Phe Lys

1315

1320

1325

5 Gly Ser Phe Arg Pro Ile Trp Val Thr Leu Asp Thr Glu Asp His Lys

1330

1335

1340

Ala Lys Ile Phe Gln Val Val Pro Ile Pro Val Val Lys Lys Lys Lys

1345

1350

1355

1360

Leu

10

<210> 109

<211> 469

15 <212> PRT

<213> Homo sapiens

<400> 109

Met His Ser Phe Pro Pro Leu Leu Leu Leu Leu Phe Trp Gly Val Val

20

1

5

10

15

Ser His Ser Phe Pro Ala Thr Leu Glu Thr Gln Glu Gln Asp Val Asp

20

25

30

Leu Val Gln Lys Tyr Leu Glu Lys Tyr Tyr Asn Leu Lys Asn Asp Gly

35

40

45

25 Arg Gln Val Glu Lys Arg Arg Asn Ser Gly Pro Val Val Glu Lys Leu

50

55

60

Lys Gln Met Gln Glu Phe Phe Gly Leu Lys Val Thr Gly Lys Pro Asp

65

70

75

80

Ala Glu Thr Leu Lys Val Met Lys Gln Pro Arg Cys Gly Val Pro Asp

358

	85	90	95
	Val Ala Gln Phe Val Leu Thr Glu Gly Asn Pro Arg Trp Glu Gln Thr		
	100	105	110
	His Leu Thr Tyr Arg Ile Glu Asn Tyr Thr Pro Asp Leu Pro Arg Ala		
5	115	120	125
	Asp Val Asp His Ala Ile Glu Lys Ala Phe Gln Leu Trp Ser Asn Val		
	130	135	140
	Thr Pro Leu Thr Phe Thr Lys Val Ser Glu Gly Gln Ala Asp Ile Met		
	145	150	155
			160
10	Ile Ser Phe Val Arg Gly Asp His Arg Asp Asn Ser Pro Phe Asp Gly		
	165	170	175
	Pro Gly Gly Asn Leu Ala His Ala Phe Gln Pro Gly Pro Gly Ile Gly		
	180	185	190
	Gly Asp Ala His Phe Asp Glu Asp Glu Arg Trp Thr Asn Asn Phe Arg		
15	195	200	205
	Glu Tyr Asn Leu His Arg Val Ala Ala His Glu Leu Gly His Ser Leu		
	210	215	220
	Gly Leu Ser His Ser Thr Asp Ile Gly Ala Leu Met Tyr Pro Ser Tyr		
	225	230	235
			240
20	Thr Phe Ser Gly Asp Val Gln Leu Ala Gln Asp Asp Ile Asp Gly Ile		
	245	250	255
	Gln Ala Ile Tyr Gly Arg Ser Gln Asn Pro Val Gln Pro Ile Gly Pro		
	260	265	270
	Gln Thr Pro Lys Ala Cys Asp Ser Lys Leu Thr Phe Asp Ala Ile Thr		
25	275	280	285
	Thr Ile Arg Gly Glu Val Met Phe Phe Lys Asp Arg Phe Tyr Met Arg		
	290	295	300
	Thr Asn Pro Phe Tyr Pro Glu Val Glu Leu Asn Phe Ile Ser Val Phe		
	305	310	315
			320
		359	

Trp Pro Gln Leu Pro Asn Gly Leu Glu Ala Ala Tyr Glu Phe Ala Asp  
 325 330 335  
 Arg Asp Glu Val Arg Phe Phe Lys Gly Asn Lys Tyr Trp Ala Val Gln  
 340 345 350  
 5 Gly Gln Asn Val Leu His Gly Tyr Pro Lys Asp Ile Tyr Ser Ser Phe  
 355 360 365  
 Gly Phe Pro Arg Thr Val Lys His Ile Asp Ala Ala Leu Ser Glu Glu  
 370 375 380  
 Asn Thr Gly Lys Thr Tyr Phe Phe Val Ala Asn Lys Tyr Trp Arg Tyr  
 10 385 390 395 400  
 Asp Glu Tyr Lys Arg Ser Met Asp Pro Gly Tyr Pro Lys Met Ile Ala  
 405 410 415  
 His Asp Phe Pro Gly Ile Gly His Lys Val Asp Ala Val Phe Met Lys  
 420 425 430  
 15 Asp Gly Phe Phe Tyr Phe Phe His Gly Thr Arg Gln Tyr Lys Phe Asp  
 435 440 445  
 Pro Lys Thr Lys Arg Ile Leu Thr Leu Gln Lys Ala Asn Ser Trp Phe  
 450 455 460  
 Asn Cys Arg Lys Asn  
 20 465

<210> 110

<211> 267

25 <212> PRT

<213> Homo sapiens

<400> 110

Met Arg Leu Thr Val Leu Cys Ala Val Cys Leu Leu Pro Gly Ser Leu  
 360

1	5	10	15
Ala Leu Pro Leu Pro Gln Glu Ala Gly Gly Met Ser Glu Leu Gln Trp			
	20	25	30
Glu Gln Ala Gln Asp Tyr Leu Lys Arg Phe Tyr Leu Tyr Asp Ser Glu			
5	35	40	45
Thr Lys Asn Ala Asn Ser Leu Glu Ala Lys Leu Lys Glu Met Gln Lys			
	50	55	60
Phe Phe Gly Leu Pro Ile Thr Gly Met Leu Asn Ser Arg Val Ile Glu			
65	70	75	80
10	Ile Met Gln Lys Pro Arg Cys Gly Val Pro Asp Val Ala Glu Tyr Ser		
	85	90	95
Leu Phe Pro Asn Ser Pro Lys Trp Thr Ser Lys Val Val Thr Tyr Arg			
	100	105	110
Ile Val Ser Tyr Thr Arg Asp Leu Pro His Ile Thr Val Asp Arg Leu			
15	115	120	125
Val Ser Lys Ala Leu Asn Met Trp Gly Lys Glu Ile Pro Leu His Phe			
	130	135	140
Arg Lys Val Val Trp Gly Thr Ala Asp Ile Met Ile Gly Phe Ala Arg			
145	150	155	160
20	Gly Ala His Gly Asp Ser Tyr Pro Phe Asp Gly Pro Gly Asn Thr Leu		
	165	170	175
Ala His Ala Phe Ala Pro Gly Thr Gly Leu Gly Gly Asp Ala His Phe			
	180	185	190
Asp Glu Asp Glu Arg Trp Thr Asp Gly Ser Ser Leu Gly Ile Asn Phe			
25	195	200	205
Leu Tyr Ala Ala Thr His Glu Leu Gly His Ser Leu Gly Met Gly His			
	210	215	220
Ser Ser Asp Pro Asn Ala Val Met Tyr Pro Thr Tyr Gly Asn Gly Asp			
225	230	235	240
361			

Pro Gln Asn Phe Lys Leu Ser Gln Asp Asp Ile Lys Gly Ile Gln Lys

245

250

255

Leu Tyr Gly Lys Arg Ser Asn Ser Arg Lys Lys

260

265

5

<210> 111

<211> 216

<212> PRT

10 <213> Homo sapiens

<400> 111

Met Arg Pro Arg Ser Gly Pro Thr Arg Asn Pro Arg Leu Arg Ala Phe

1

5

10

15

15 Ala Gly Val Pro Thr Arg Gly Arg Thr Arg Gly Gln Ser Arg Arg Cys

20

25

30

Ala Ala Glu Ala Ser Ala Gly Pro Glu Arg Asp Ala Arg Pro Gly Ala

35

40

45

Pro Ala Ala Gly Thr Met Gly Ala Ala His Ser Ala Ser Glu Glu Val

20 50

55

60

Arg Glu Leu Glu Gly Lys Thr Gly Phe Ser Ser Asp Gln Ile Glu Gln

65

70

75

80

Leu His Arg Arg Phe Lys Gln Leu Ser Gly Asp Gln Pro Thr Ile Arg

85

90

95

25 Lys Glu Asn Phe Asn Asn Val Pro Asp Leu Glu Leu Asn Pro Ile Arg

100

105

110

Ser Lys Ile Val Arg Ala Phe Phe Asp Asn Arg Asn Leu Arg Lys Gly

115

120

125

Pro Ser Gly Leu Ala Asp Glu Ile Asn Phe Glu Asp Phe Leu Thr Ile

362

130                      135                      140  
 Met Ser Tyr Phe Arg Pro Ile Asp Thr Thr Met Asp Glu Glu Gln Val  
 145                      150                      155                      160  
 Glu Leu Ser Arg Lys Glu Lys Leu Arg Phe Leu Phe His Met Tyr Asp  
 5                      165                      170                      175  
 Ser Asp Ser Asp Gly Arg Ile Thr Leu Glu Glu Tyr Arg Asn Val Lys  
                     180                      185                      190  
 Trp Ser Arg Ser Cys Cys Arg Glu Thr Leu Thr Ser Arg Arg Ser Pro  
                     195                      200                      205  
 10 Leu Ala Pro Ser Pro Thr Gly Pro  
                     210                      215

<210> 112

15 <211> 422

<212> PRT

<213> Homo sapiens

<400> 112

20 Met Asn Ser Gly His Ser Phe Ser Gln Thr Pro Ser Ala Ser Phe His  
     1                      5                      10                      15  
 Gly Ala Gly Gly Gly Trp Gly Arg Pro Arg Ser Phe Pro Arg Ala Pro  
                     20                      25                      30  
 Thr Val His Gly Gly Ala Gly Gly Ala Arg Ile Ser Leu Ser Phe Thr  
 25                      35                      40                      45  
 Thr Arg Ser Cys Pro Pro Pro Gly Gly Ser Trp Gly Ser Gly Arg Ser  
                     50                      55                      60  
 Ser Pro Leu Leu Gly Gly Asn Gly Lys Ala Thr Met Gln Asn Leu Asn  
 65                      70                      75                      80



Asp Arg Leu Ala Ser Tyr Val Glu Lys Val Arg Ala Leu Glu Glu Ala  
 85 90 95  
 Asn Met Lys Leu Glu Ser Arg Ile Leu Lys Trp His Gln Gln Arg Asp  
 100 105 110  
 5 Pro Gly Ser Lys Lys Asp Tyr Ser Gln Tyr Glu Glu Asn Ile Thr His  
 115 120 125  
 Leu Gln Glu Gln Ile Val Asp Gly Lys Met Thr Asn Ala Gln Ile Ile  
 130 135 140  
 Leu Leu Ile Asp Asn Ala Arg Met Ala Val Asp Asp Phe Asn Leu Lys  
 10 145 150 155 160  
 Tyr Glu Asn Glu His Ser Phe Lys Lys Asp Leu Glu Ile Glu Val Glu  
 165 170 175  
 Gly Leu Arg Arg Thr Leu Asp Asn Leu Thr Ile Val Thr Thr Asp Leu  
 180 185 190  
 15 Glu Gln Glu Val Glu Gly Met Arg Lys Glu Leu Ile Leu Met Lys Lys  
 195 200 205  
 His His Glu Gln Glu Met Glu Lys His His Val Pro Ser Asp Phe Asn  
 210 215 220  
 Val Asn Val Lys Val Asp Thr Gly Pro Arg Glu Asp Leu Ile Lys Val  
 20 225 230 235 240  
 Leu Glu Asp Met Arg Gln Glu Tyr Glu Leu Ile Ile Lys Lys Lys His  
 245 250 255  
 Arg Asp Leu Asp Thr Trp Tyr Lys Glu Gln Ser Ala Ala Met Ser Gln  
 260 265 270  
 25 Glu Ala Ala Ser Pro Ala Thr Val Gln Ser Arg Gln Gly Asp Ile His  
 275 280 285  
 Glu Leu Lys Arg Thr Phe Gln Ala Leu Glu Ile Asp Leu Gln Thr Gln  
 290 295 300  
 Tyr Ser Thr Lys Ser Ala Leu Glu Asn Met Leu Ser Glu Thr Gln Ser  
 364



Ser Arg Thr Asn Glu Asn Asp Pro Ala Lys His Gly Asp Gln His Glu  
 50 55 60  
 Gly Gln His Tyr Asn Ile Ser Pro Gln Asp Leu Glu Thr Val Phe Pro  
 65 70 75 80  
 5 His Gly Leu Pro Pro Arg Phe Val Met Gln Val Lys Thr Phe Ser Glu  
 85 90 95  
 Ala Cys Leu Met Val Arg Lys Pro Ala Leu Glu Leu Leu His Tyr Leu  
 100 105 110  
 Lys Asn Thr Ser Phe Ala Tyr Pro Ala Ile Arg Tyr Leu Leu Tyr Gly  
 10 115 120 125  
 Glu Lys Gly Thr Gly Lys Thr Leu Ser Leu Cys His Val Ile His Phe  
 130 135 140  
 Cys Ala Lys Gln Asp Trp Leu Ile Leu His Ile Pro Asp Ala His Leu  
 145 150 155 160  
 15 Trp Val Lys Asn Cys Arg Asp Leu Leu Gln Ser Ser Tyr Asn Lys Gln  
 165 170 175  
 Arg Phe Asp Gln Pro Leu Glu Ala Ser Thr Trp Leu Lys Asn Phe Lys  
 180 185 190  
 Thr Thr Asn Glu Arg Phe Leu Asn Gln Ile Lys Val Gln Glu Lys Tyr  
 20 195 200 205  
 Val Trp Asn Lys Arg Glu Ser Thr Glu Lys Gly Ser Pro Leu Gly Glu  
 210 215 220  
 Val Val Glu Gln Gly Ile Thr Arg Val Arg Asn Ala Thr Asp Ala Val  
 225 230 235 240  
 25 Gly Ile Val Leu Lys Glu Leu Lys Arg Gln Ser Ser Leu Gly Met Phe  
 245 250 255  
 His Leu Leu Val Ala Val Asp Gly Ile Asn Ala Leu Trp Gly Arg Thr  
 260 265 270  
 Thr Leu Lys Arg Glu Asp Lys Ser Pro Ile Ala Pro Glu Glu Leu Ala  
 366

	275	280	285
	Leu Val His Asn Leu Arg Lys Met Met Lys Asn Asp Trp His Gly Gly		
	290	295	300
	Ala Ile Val Ser Ala Leu Ser Gln Thr Gly Ser Leu Phe Lys Pro Arg		
5	305	310	315 320
	Lys Ala Tyr Leu Pro Gln Glu Leu Leu Gly Lys Glu Gly Phe Asp Ala		
	325	330	335
	Leu Asp Pro Phe Ile Pro Ile Leu Val Ser Asn Tyr Asn Pro Lys Glu		
	340	345	350
10	Phe Glu Ser Cys Ile Gln Tyr Tyr Leu Glu Asn Asn Trp Leu Gln His		
	355	360	365
	Glu Lys Ala Pro Thr Glu Glu Gly Lys Lys Glu Leu Leu Phe Leu Ser		
	370	375	380
	Asn Ala Asn Pro Ser Leu Leu Glu Arg His Cys Ala Tyr Leu		
15	385	390	395

<210> 114

<211> 75

20 <212> PRT

<213> Homo sapiens

<400> 114

	Met Leu Ser His Phe Arg Val Lys Val Lys Gly Phe Ile Leu Ile Ser
25	1 5 10 15
	Lys Tyr Phe Asp Pro Tyr Asp Leu Val Ser Ser Tyr Pro Lys Tyr Gly
	20 25 30
	Pro His Thr Ser Arg Thr Gly Ile Leu Trp Glu Leu Val Arg Asn Val
	35 40 45
	367

Glu Ser Leu Val Leu Arg Phe Ser Lys Ser Glu Ser Ala Phe Ser Ser

50

55

60

Ala Leu Leu Ala Ile His Met Phe Glu Lys Asp

65

70

75

5

<210> 115

<211> 163

<212> PRT

10 <213> Homo sapiens

<400> 115

Met Ser Glu Ser Gly Phe Lys Leu Leu Cys Gln Cys Leu Gly Phe Gly

1

5

10

15

15 Ser Gly His Phe Arg Cys Asp Ser Ser Arg Trp Cys His Asp Asn Gly

20

25

30

Val Asn Tyr Lys Ile Gly Glu Lys Trp Asp Arg Gln Gly Glu Asn Gly

35

40

45

Gln Met Met Ser Cys Thr Cys Leu Gly Asn Gly Lys Gly Glu Phe Lys

20

50

55

60

Cys Asp Pro His Glu Ala Thr Cys Tyr Asp Asp Gly Lys Thr Tyr His

65

70

75

80

Val Gly Glu Gln Trp Gln Lys Glu Tyr Leu Gly Ala Ile Cys Ser Cys

85

90

95

25 Thr Cys Phe Gly Gly Gln Arg Gly Trp Arg Cys Asp Asn Cys Arg Arg

100

105

110

Pro Gly Gly Glu Pro Ser Pro Glu Gly Thr Thr Gly Gln Ser Tyr Asn

115

120

125

Gln Tyr Ser Gln Arg Tyr His Gln Arg Thr Asn Thr Asn Val Asn Cys

368

130                      135                      140  
 Pro Ile Glu Cys Phe Met Pro Leu Asp Val Gln Ala Asp Arg Glu Asp  
 145                      150                      155                      160  
 Ser Arg Glu  
 5  
  
 <210> 116  
 <211> 483  
 10 <212> PRT  
 <213> Homo sapiens  
  
 <400> 116  
 Met Ser Ile Arg Val Thr Gln Lys Ser Tyr Lys Val Ser Thr Ser Gly  
 15    1                      5                      10                      15  
 Pro Arg Ala Phe Ser Ser Arg Ser Tyr Thr Ser Gly Pro Gly Ser Arg  
                     20                      25                      30  
 Ile Ser Ser Ser Ser Phe Ser Arg Val Gly Ser Ser Asn Phe Arg Gly  
                     35                      40                      45  
 20 Gly Leu Gly Gly Gly Tyr Gly Gly Ala Ser Gly Met Gly Gly Ile Thr  
                     50                      55                      60  
 Ala Val Thr Val Asn Gln Ser Leu Leu Ser Pro Leu Val Leu Glu Val  
 65                      70                      75                      80  
 Asp Pro Asn Ile Gln Ala Val Arg Thr Gln Glu Lys Glu Gln Ile Lys  
 25                      85                      90                      95  
 Thr Leu Asn Asn Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu  
                     100                      105                      110  
 Glu Gln Gln Asn Lys Met Leu Glu Thr Lys Trp Ser Leu Leu Gln Gln  
                     115                      120                      125  
 369

Gln Lys Thr Ala Arg Ser Asn Met Asp Asn Met Phe Glu Ser Tyr Ile  
 130 135 140  
 Asn Asn Leu Arg Arg Gln Leu Glu Thr Leu Gly Gln Glu Lys Leu Lys  
 145 150 155 160  
 5 Leu Glu Ala Glu Leu Gly Asn Met Gln Gly Leu Val Glu Asp Phe Lys  
 165 170 175  
 Asn Lys Tyr Glu Asp Glu Ile Asn Lys Arg Thr Glu Met Glu Asn Glu  
 180 185 190  
 Phe Val Leu Ile Lys Lys Asp Val Asp Glu Ala Tyr Met Asn Lys Val  
 10 195 200 205  
 Glu Leu Glu Ser Arg Leu Glu Gly Leu Thr Asp Glu Ile Asn Phe Leu  
 210 215 220  
 Arg Gln Leu Tyr Glu Glu Glu Ile Arg Glu Leu Gln Ser Gln Ile Ser  
 225 230 235 240  
 15 Asp Thr Ser Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp Met  
 245 250 255  
 Asp Ser Ile Ile Ala Glu Val Lys Ala Gln Tyr Glu Asp Ile Ala Asn  
 260 265 270  
 Arg Ser Arg Ala Glu Ala Glu Ser Met Tyr Gln Ile Lys Tyr Glu Glu  
 20 275 280 285  
 Leu Gln Ser Leu Ala Gly Lys His Gly Asp Asp Leu Arg Arg Thr Lys  
 290 295 300  
 Thr Glu Ile Ser Glu Met Asn Arg Asn Ile Ser Arg Leu Gln Ala Glu  
 305 310 315 320  
 25 Ile Glu Gly Leu Lys Gly Gln Arg Ala Ser Leu Glu Ala Ala Ile Ala  
 325 330 335  
 Asp Ala Glu Gln Arg Gly Glu Leu Ala Ile Lys Asp Ala Asn Ala Lys  
 340 345 350  
 Leu Ser Glu Leu Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met Ala  
 370

	355		360		365
	Arg Gln Leu Arg Glu Tyr Gln Glu Leu Met Asn Val Lys Leu Ala Leu				
	370		375		380
	Asp Ile Glu Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Ser				
5	385		390		395 400
	Arg Leu Glu Ser Gly Met Gln Asn Met Ser Ile His Thr Lys Thr Thr				
		405		410	415
	Ser Gly Tyr Ala Gly Gly Leu Ser Ser Ala Tyr Gly Gly Leu Thr Ser				
	420		425		430
10	Pro Gly Leu Ser Tyr Ser Leu Gly Ser Ser Phe Gly Ser Gly Ala Gly				
	435		440		445
	Ser Ser Ser Phe Ser Arg Thr Ser Ser Ser Arg Ala Val Val Val Lys				
	450		455		460
	Lys Ile Glu Thr Arg Asp Gly Lys Leu Val Ser Glu Ser Ser Asp Val				
15	465		470		475 480
	Leu Pro Lys				

20 <210> 117  
 <211> 430  
 <212> PRT  
 <213> Homo sapiens

25 <400> 117

Met Ser Phe Thr Thr Arg Ser Thr Phe Ser Thr Asn Tyr Arg Ser Leu				
1		5		10 15
Gly Ser Val Gln Ala Pro Ser Tyr Gly Ala Arg Pro Val Ser Ser Ala				
	20		25	30
			371	



Ala Ser Val Tyr Ala Gly Ala Gly Gly Ser Gly Ser Arg Ile Ser Val  
 35 40 45  
 Ser Arg Ser Thr Ser Phe Arg Gly Gly Met Gly Ser Gly Gly Leu Ala  
 50 55 60  
 5 Thr Gly Ile Ala Gly Gly Leu Ala Gly Met Gly Gly Ile Gln Asn Glu  
 65 70 75 80  
 Lys Glu Thr Met Gln Ser Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp  
 85 90 95  
 Arg Val Arg Ser Leu Glu Thr Glu Asn Arg Arg Leu Glu Ser Lys Ile  
 10 100 105 110  
 Arg Glu His Leu Glu Lys Lys Gly Pro Gln Val Arg Asp Trp Ser His  
 115 120 125  
 Tyr Phe Lys Ile Ile Glu Asp Leu Arg Ala Gln Ile Phe Ala Asn Thr  
 130 135 140  
 15 Val Asp Asn Ala Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu Ala  
 145 150 155 160  
 Ala Asp Asp Phe Arg Val Lys Tyr Glu Thr Glu Leu Ala Met Arg Gln  
 165 170 175  
 Ser Val Glu Asn Asp Ile His Gly Leu Arg Lys Val Ile Asp Asp Thr  
 20 180 185 190  
 Asn Ile Thr Arg Leu Gln Leu Glu Thr Glu Ile Glu Ala Leu Lys Glu  
 195 200 205  
 Glu Leu Leu Phe Met Lys Lys Asn His Glu Glu Glu Val Lys Gly Leu  
 210 215 220  
 25 Gln Ala Gln Ile Ala Ser Ser Gly Leu Thr Val Glu Val Asp Ala Pro  
 225 230 235 240  
 Lys Ser Gln Asp Leu Ala Lys Ile Met Ala Asp Ile Arg Ala Gln Tyr  
 245 250 255  
 Asp Glu Leu Ala Arg Lys Asn Arg Glu Glu Leu Asp Lys Tyr Trp Ser  
 372

	260	265	270
	Gln Gln Ile Glu Glu Ser Thr Thr Val Val Thr Thr Gln Ser Ala Glu		
	275	280	285
	Val Gly Ala Ala Glu Thr Thr Leu Thr Glu Leu Arg Arg Thr Val Gln		
5	290	295	300
	Ser Leu Glu Ile Asp Leu Asp Ser Met Arg Asn Leu Lys Ala Ser Leu		
	305	310	315 320
	Glu Asn Ser Leu Arg Glu Val Glu Ala Arg Tyr Ala Leu Gln Met Glu		
	325	330	335
10	Gln Leu Asn Gly Ile Leu Leu His Leu Glu Ser Glu Leu Ala Gln Thr		
	340	345	350
	Arg Ala Glu Gly Gln Arg Gln Ala Gln Glu Tyr Glu Ala Leu Leu Asn		
	355	360	365
	Ile Lys Val Lys Leu Glu Ala Glu Ile Ala Thr Tyr Arg Arg Leu Leu		
15	370	375	380
	Glu Asp Gly Glu Asp Phe Asn Leu Gly Asp Ala Leu Asp Ser Ser Asn		
	385	390	395 400
	Ser Met Gln Thr Ile Gln Lys Thr Thr Thr Arg Arg Ile Val Asp Gly		
	405	410	415
20	Lys Val Val Ser Glu Thr Asn Asp Thr Lys Val Leu Arg His		
	420	425	430

<210> 118

25 <211> 400

<212> PRT

<213> Homo sapiens

<400> 118

Met Thr Ser Tyr Ser Tyr Arg Gln Ser Ser Ala Thr Ser Ser Phe Gly  
 1 5 10 15  
 Gly Leu Gly Gly Gly Ser Val Arg Phe Gly Pro Gly Val Ala Phe Arg  
 20 25 30  
 5 Ala Pro Ser Ile His Gly Gly Ser Gly Gly Arg Gly Val Ser Val Ser  
 35 40 45  
 Ser Ala Arg Phe Val Ser Ser Ser Ser Ser Gly Ala Tyr Gly Gly Gly  
 50 55 60  
 Tyr Gly Gly Val Leu Thr Ala Ser Asp Gly Leu Leu Ala Gly Asn Glu  
 10 65 70 75 80  
 Lys Leu Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp  
 85 90 95  
 Lys Val Arg Ala Leu Glu Ala Ala Asn Gly Glu Leu Glu Val Lys Ile  
 100 105 110  
 15 Arg Asp Trp Tyr Gln Lys Gln Gly Pro Gly Pro Ser Arg Asp Tyr Ser  
 115 120 125  
 His Tyr Tyr Thr Thr Ile Gln Asp Leu Arg Asp Lys Ile Leu Gly Ala  
 130 135 140  
 Thr Ile Glu Asn Ser Arg Ile Val Leu Gln Ile Asp Asn Ala Arg Leu  
 20 145 150 155 160  
 Ala Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg  
 165 170 175  
 Met Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu  
 180 185 190  
 25 Leu Thr Leu Ala Arg Thr Asp Leu Glu Met Gln Ile Glu Gly Leu Lys  
 195 200 205  
 Glu Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Ile Ser Thr  
 210 215 220  
 Leu Arg Gly Gln Val Gly Gly Gln Val Ser Val Glu Val Asp Ser Ala  
 374

225                      230                      235                      240  
 Pro Gly Thr Asp Leu Ala Lys Ile Leu Ser Asp Met Arg Ser Gln Tyr  
                          245                      250                      255  
 Glu Val Met Ala Glu Gln Asn Arg Lys Asp Ala Glu Ala Trp Phe Thr  
 5                      260                      265                      270  
 Ser Arg Thr Glu Glu Leu Asn Arg Glu Val Ala Gly His Thr Glu Gln  
                          275                      280                      285  
 Leu Gln Met Ser Arg Ser Glu Val Thr Asp Leu Arg Arg Thr Leu Gln  
                          290                      295                      300  
 10 Gly Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ala Leu  
                          305                      310                      315                      320  
 Glu Asp Thr Leu Ala Glu Thr Glu Ala Arg Phe Gly Ala Gln Leu Ala  
                          325                      330                      335  
 His Ile Gln Ala Leu Ile Ser Gly Ile Glu Ala Gln Leu Gly Asp Val  
 15                      340                      345                      350  
 Arg Ala Asp Ser Glu Arg Gln Asn Gln Glu Tyr Gln Arg Leu Met Asp  
                          355                      360                      365  
 Ile Lys Ser Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Ser Leu Leu  
                          370                      375                      380  
 20 Glu Gly Gln Glu Asp His Tyr Asn Asn Leu Ser Ala Ser Lys Val Leu  
                          385                      390                      395                      400

<210> 119

25 <211> 424

<212> PRT

<213> Homo sapiens

<400> 119

Met Asp Phe Ser Arg Arg Ser Phe His Arg Ser Leu Ser Ser Ser Leu  
 1 5 10 15  
 Gln Ala Pro Val Val Ser Thr Val Gly Met Gln Arg Leu Gly Thr Thr  
 20 25 30  
 5 Pro Ser Val Tyr Gly Gly Ala Gly Gly Arg Gly Ile Arg Ile Ser Asn  
 35 40 45  
 Ser Arg His Thr Val Asn Tyr Gly Ser Asp Leu Thr Gly Gly Gly Asp  
 50 55 60  
 Leu Phe Val Gly Asn Glu Lys Met Ala Met Gln Asn Leu Asn Asp Arg  
 10 65 70 75 80  
 Leu Ala Ser Tyr Leu Glu Lys Val Arg Thr Leu Glu Gln Ser Asn Ser  
 85 90 95  
 Lys Leu Glu Val Gln Ile Lys Gln Trp Tyr Glu Thr Asn Ala Pro Arg  
 100 105 110  
 15 Ala Gly Arg Asp Tyr Ser Ala Tyr Tyr Arg Gln Ile Glu Glu Leu Arg  
 115 120 125  
 Ser Gln Ile Lys Asp Ala Gln Leu Gln Asn Ala Arg Cys Val Leu Gln  
 130 135 140  
 Ile Asp Asn Ala Lys Leu Ala Ala Glu Asp Phe Arg Leu Lys Tyr Glu  
 20 145 150 155 160  
 Thr Glu Arg Gly Ile Arg Leu Thr Val Glu Ala Asp Leu Gln Gly Leu  
 165 170 175  
 Asn Lys Val Phe Asp Asp Leu Thr Leu His Lys Thr Asp Leu Glu Ile  
 180 185 190  
 25 Gln Ile Glu Glu Leu Asn Lys Asp Leu Ala Leu Leu Lys Lys Glu His  
 195 200 205  
 Gln Glu Glu Val Asp Gly Leu His Lys His Leu Gly Asn Thr Val Asn  
 210 215 220  
 Val Glu Val Asp Ala Ala Pro Gly Leu Asn Leu Gly Val Ile Met Asn  
 376

225	230	235	240
Glu Met Arg Gln Lys Tyr Glu Val Met Ala Gln Lys Asn Leu Gln Glu			
245	250	255	
Ala Lys Glu Gln Phe Glu Arg Gln Thr Ala Val Leu Gln Gln Gln Val			
5	260	265	270
Thr Val Asn Thr Glu Glu Leu Lys Gly Thr Glu Val Gln Leu Thr Glu			
275	280	285	
Leu Arg Arg Thr Ser Gln Ser Leu Glu Ile Glu Leu Gln Ser His Leu			
290	295	300	
10	Ser Met Lys Glu Ser Leu Glu His Thr Leu Glu Glu Thr Lys Ala Arg		
305	310	315	320
Tyr Ser Ser Gln Leu Ala Asn Leu Gln Ser Leu Leu Ser Ser Leu Glu			
325	330	335	
Ala Gln Leu Met Gln Ile Arg Ser Asn Met Glu Arg Gln Asn Asn Glu			
15	340	345	350
Tyr His Ile Leu Leu Asp Ile Lys Thr Arg Leu Glu Gln Glu Ile Ala			
355	360	365	
Thr Tyr Arg Arg Leu Leu Glu Gly Glu Asp Val Lys Thr Thr Glu Tyr			
370	375	380	
20	Gln Leu Ser Thr Leu Glu Glu Arg Asp Ile Lys Lys Thr Arg Lys Ile		
385	390	395	400
Lys Thr Val Val Gln Glu Val Val Asp Gly Lys Val Val Ser Ser Glu			
405	410	415	
Val Lys Glu Val Glu Glu Asn Ile			
25	420		

<210> 120

<211> 1255

<212> PRT

<213> Homo sapiens

<400> 120

5 Met Thr Pro Gly Thr Gln Ser Pro Phe Phe Leu Leu Leu Leu Leu Thr  
1 5 10 15  
Val Leu Thr Val Val Thr Gly Ser Gly His Ala Ser Ser Thr Pro Gly  
20 25 30  
Gly Glu Lys Glu Thr Ser Ala Thr Gln Arg Ser Ser Val Pro Ser Ser  
10 35 40 45  
Thr Glu Lys Asn Ala Val Ser Met Thr Ser Ser Val Leu Ser Ser His  
50 55 60  
Ser Pro Gly Ser Gly Ser Ser Thr Thr Gln Gly Gln Asp Val Thr Leu  
65 70 75 80  
15 Ala Pro Ala Thr Glu Pro Ala Ser Gly Ser Ala Ala Thr Trp Gly Gln  
85 90 95  
Asp Val Thr Ser Val Pro Val Thr Arg Pro Ala Leu Gly Ser Thr Thr  
100 105 110  
Pro Pro Ala His Asp Val Thr Ser Ala Pro Asp Asn Lys Pro Ala Pro  
20 115 120 125  
Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
130 135 140  
Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
145 150 155 160  
25 Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
165 170 175  
Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
180 185 190  
Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
378

	195	200	205
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	210	215	220
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
5	225	230	235 240
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	245	250	255
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
	260	265	270
10	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	275	280	285
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	290	295	300
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
15	305	310	315 320
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	325	330	335
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
	340	345	350
20	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	355	360	365
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
	370	375	380
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
25	385	390	395 400
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	405	410	415
	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
	420	425	430
		379	



Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
 435 440 445  
 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
 450 455 460  
 5 Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
 465 470 475 480  
 Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
 485 490 495  
 Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
 10 500 505 510  
 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
 515 520 525  
 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
 530 535 540  
 15 Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
 545 550 555 560  
 Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
 565 570 575  
 Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
 20 580 585 590  
 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
 595 600 605  
 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr  
 610 615 620  
 25 Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser  
 625 630 635 640  
 Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His  
 645 650 655  
 Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
 380

	660	665	670
	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	675	680	685
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
5	690	695	700
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	705	710	715 720
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	725	730	735
10	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
	740	745	750
	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	755	760	765
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
15	770	775	780
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	785	790	795 800
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	805	810	815
20	Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala		
	820	825	830
	Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro		
	835	840	845
	Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr		
25	850	855	860
	Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser		
	865	870	875 880
	Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala Pro Pro Ala His		
	885	890	895

Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro Gly Ser Thr Ala  
 900 905 910  
 Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Thr Arg Pro Ala Pro  
 915 920 925  
 5 Gly Ser Thr Ala Pro Pro Ala His Gly Val Thr Ser Ala Pro Asp Asn  
 930 935 940  
 Arg Pro Ala Leu Gly Ser Thr Ala Pro Pro Val His Asn Val Thr Ser  
 945 950 955 960  
 Ala Ser Gly Ser Ala Ser Gly Ser Ala Ser Thr Leu Val His Asn Gly  
 10 965 970 975  
 Thr Ser Ala Arg Ala Thr Thr Thr Pro Ala Ser Lys Ser Thr Pro Phe  
 980 985 990  
 Ser Ile Pro Ser His His Ser Asp Thr Pro Thr Thr Leu Ala Ser His  
 995 1000 1005  
 15 Ser Thr Lys Thr Asp Ala Ser Ser Thr His His Ser Ser Val Pro Pro  
 1010 1015 1020  
 Leu Thr Ser Ser Asn His Ser Thr Ser Pro Gln Leu Ser Thr Gly Val  
 1025 1030 1035 1040  
 Ser Phe Phe Phe Leu Ser Phe His Ile Ser Asn Leu Gln Phe Asn Ser  
 20 1045 1050 1055  
 Ser Leu Glu Asp Pro Ser Thr Asp Tyr Tyr Gln Glu Leu Gln Arg Asp  
 1060 1065 1070  
 Ile Ser Glu Met Phe Leu Gln Ile Tyr Lys Gln Gly Gly Phe Leu Gly  
 1075 1080 1085  
 25 Leu Ser Asn Ile Lys Phe Arg Pro Gly Ser Val Val Val Gln Leu Thr  
 1090 1095 1100  
 Leu Ala Phe Arg Glu Gly Thr Ile Asn Val His Asp Val Glu Thr Gln  
 1105 1110 1115 1120  
 Phe Asn Gln Tyr Lys Thr Glu Ala Ala Ser Arg Tyr Asn Leu Thr Ile  
 382

	1125	1130	1135
	Ser Asp Val Ser Val Ser Asp Val Pro Phe Pro Phe Ser Ala Gln Ser		
	1140	1145	1150
	Gly Ala Gly Val Pro Gly Trp Gly Ile Ala Leu Leu Val Leu Val Cys		
5	1155	1160	1165
	Val Leu Val Ala Leu Ala Ile Val Tyr Leu Ile Ala Leu Ala Val Cys		
	1170	1175	1180
	Gln Cys Arg Arg Lys Asn Tyr Gly Gln Leu Asp Ile Phe Pro Ala Arg		
	1185	1190	1195
			1200
10	Asp Thr Tyr His Pro Met Ser Glu Tyr Pro Thr Tyr His Thr His Gly		
	1205	1210	1215
	Arg Tyr Val Pro Pro Ser Ser Thr Asp Arg Ser Pro Tyr Glu Lys Val		
	1220	1225	1230
	Ser Ala Gly Asn Gly Gly Ser Ser Leu Ser Tyr Thr Asn Pro Ala Val		
15	1235	1240	1245
	Ala Ala Ala Ser Ala Asn Leu		
	1250	1255	

20 <210> 121  
 <211> 5179  
 <212> PRT  
 <213> Homo sapiens

25 <400> 121

Met Gly Leu Pro Leu Ala Arg Leu Ala Ala Val Cys Leu Ala Leu Ser
1                      5                      10                      15
Leu Ala Gly Gly Ser Glu Leu Gln Thr Glu Gly Arg Thr Arg Tyr His
20                      25                      30
383

Gly Arg Asn Val Cys Ser Thr Trp Gly Asn Phe His Tyr Lys Thr Phe  
 35 40 45  
 Asp Gly Asp Val Phe Arg Phe Pro Gly Leu Cys Asp Tyr Asn Phe Ala  
 50 55 60  
 5 Ser Asp Cys Arg Gly Ser Tyr Lys Glu Phe Ala Val His Leu Lys Arg  
 65 70 75 80  
 Gly Pro Gly Gln Ala Glu Ala Pro Ala Gly Val Glu Ser Ile Leu Leu  
 85 90 95  
 Thr Ile Lys Asp Asp Thr Ile Tyr Leu Thr Arg His Leu Ala Val Leu  
 10 100 105 110  
 Asn Gly Ala Val Val Ser Thr Pro His Tyr Ser Pro Gly Leu Leu Ile  
 115 120 125  
 Glu Lys Ser Asp Ala Tyr Thr Lys Val Tyr Ser Arg Ala Gly Leu Thr  
 130 135 140  
 15 Leu Met Trp Asn Arg Glu Asp Ala Leu Met Leu Glu Leu Asp Thr Lys  
 145 150 155 160  
 Phe Arg Asn His Thr Cys Gly Leu Cys Gly Asp Tyr Asn Gly Leu Gln  
 165 170 175  
 Ser Tyr Ser Glu Phe Leu Ser Asp Gly Val Leu Phe Ser Pro Leu Glu  
 20 180 185 190  
 Phe Gly Asn Met Gln Lys Ile Asn Gln Pro Asp Val Val Cys Glu Asp  
 195 200 205  
 Pro Glu Glu Glu Val Ala Pro Ala Ser Cys Ser Glu His Arg Ala Glu  
 210 215 220  
 25 Cys Glu Arg Leu Leu Thr Ala Glu Ala Phe Ala Asp Cys Gln Asp Leu  
 225 230 235 240  
 Val Pro Leu Glu Pro Tyr Leu Arg Ala Cys Gln Gln Asp Arg Cys Arg  
 245 250 255  
 Cys Pro Gly Gly Asp Thr Cys Val Cys Ser Thr Val Ala Glu Phe Ser  
 384

	260	265	270
	Arg Gln Cys Ser His Ala Gly Gly Arg Pro Gly Asn Trp Arg Thr Ala		
	275	280	285
	Thr Leu Cys Pro Lys Thr Cys Pro Gly Asn Leu Val Tyr Leu Glu Ser		
5	290	295	300
	Gly Ser Pro Cys Met Asp Thr Cys Ser His Leu Glu Val Ser Ser Leu		
	305	310	315 320
	Cys Glu Glu His Arg Met Asp Gly Cys Phe Cys Pro Glu Gly Thr Val		
	325	330	335
10	Tyr Asp Asp Ile Gly Asp Ser Gly Cys Val Pro Val Ser Gln Cys His		
	340	345	350
	Cys Arg Leu His Gly His Leu Tyr Thr Pro Gly Gln Glu Ile Thr Asn		
	355	360	365
	Asp Cys Glu Gln Cys Val Cys Asn Ala Gly Arg Trp Val Cys Lys Asp		
15	370	375	380
	Leu Pro Cys Pro Gly Thr Cys Ala Leu Glu Gly Gly Ser His Ile Thr		
	385	390	395 400
	Thr Phe Asp Gly Lys Thr Tyr Thr Phe His Gly Asp Cys Tyr Tyr Val		
	405	410	415
20	Leu Ala Lys Gly Asp His Asn Asp Ser Tyr Ala Leu Leu Gly Glu Leu		
	420	425	430
	Ala Pro Cys Gly Ser Thr Asp Lys Gln Thr Cys Leu Lys Thr Val Val		
	435	440	445
	Leu Leu Ala Asp Lys Lys Lys Asn Ala Val Val Phe Lys Ser Asp Gly		
25	450	455	460
	Ser Val Leu Leu Asn Gln Leu Gln Val Asn Leu Pro His Val Thr Ala		
	465	470	475 480
	Ser Phe Ser Val Phe Arg Pro Ser Ser Tyr His Ile Met Val Ser Met		
	485	490	495
		385	

Ala Ile Gly Val Arg Leu Gln Val Gln Leu Ala Pro Val Met Gln Leu  
 500 505 510  
 Phe Val Thr Leu Asp Gln Ala Ser Gln Gly Gln Val Gln Gly Leu Cys  
 515 520 525  
 5 Gly Asn Phe Asn Gly Leu Glu Gly Asp Asp Phe Lys Thr Ala Ser Gly  
 530 535 540  
 Leu Val Glu Ala Thr Gly Ala Gly Phe Ala Asn Thr Trp Lys Ala Gln  
 545 550 555 560  
 Ser Thr Cys His Asp Lys Leu Asp Trp Leu Asp Asp Pro Cys Ser Leu  
 10 565 570 575  
 Asn Ile Glu Ser Ala Asn Tyr Ala Glu His Trp Cys Ser Leu Leu Lys  
 580 585 590  
 Lys Thr Glu Thr Pro Phe Gly Arg Cys His Ser Ala Val Asp Pro Ala  
 595 600 605  
 15 Glu Tyr Tyr Lys Arg Cys Lys Tyr Asp Thr Cys Asn Cys Gln Asn Asn  
 610 615 620  
 Glu Asp Cys Leu Cys Ala Ala Leu Ser Ser Tyr Ala Arg Ala Cys Thr  
 625 630 635 640  
 Ala Lys Gly Val Met Leu Trp Gly Trp Arg Glu His Val Cys Asn Lys  
 20 645 650 655  
 Asp Val Gly Ser Cys Pro Asn Ser Gln Val Phe Leu Tyr Asn Leu Thr  
 660 665 670  
 Thr Cys Gln Gln Thr Cys Arg Ser Leu Ser Glu Ala Asp Ser His Cys  
 675 680 685  
 25 Leu Glu Gly Phe Ala Pro Val Asp Gly Cys Gly Cys Pro Asp His Thr  
 690 695 700  
 Phe Leu Asp Glu Lys Gly Arg Cys Val Pro Leu Ala Lys Cys Ser Cys  
 705 710 715 720  
 Tyr His Arg Gly Leu Tyr Leu Glu Ala Gly Asp Val Val Val Arg Gln  
 386

	725	730	735
	Glu Glu Arg Cys Val Cys Arg Asp Gly Arg Leu His Cys Arg Gln Ile		
	740	745	750
	Arg Leu Ile Gly Gln Ser Cys Thr Ala Pro Lys Ile His Met Asp Cys		
5	755	760	765
	Ser Asn Leu Thr Ala Leu Ala Thr Ser Lys Pro Arg Ala Leu Ser Cys		
	770	775	780
	Gln Thr Leu Ala Ala Gly Tyr Tyr His Thr Glu Cys Val Ser Gly Cys		
	785	790	800
10	Val Cys Pro Asp Gly Leu Met Asp Asp Gly Arg Gly Gly Cys Val Val		
	805	810	815
	Glu Lys Glu Cys Pro Cys Val His Asn Asn Asp Leu Tyr Ser Ser Gly		
	820	825	830
	Ala Lys Ile Lys Val Asp Cys Asn Thr Cys Thr Cys Lys Arg Gly Arg		
15	835	840	845
	Trp Val Cys Thr Gln Ala Val Cys His Gly Thr Cys Ser Ile Tyr Gly		
	850	855	860
	Ser Gly His Tyr Ile Thr Phe Asp Gly Lys Tyr Tyr Asp Phe Asp Gly		
	865	870	880
20	His Cys Ser Tyr Val Ala Val Gln Asp Tyr Cys Gly Gln Asn Ser Ser		
	885	890	895
	Leu Gly Ser Phe Ser Ile Ile Thr Glu Asn Val Pro Cys Gly Thr Thr		
	900	905	910
	Gly Val Thr Cys Ser Lys Ala Ile Lys Ile Phe Met Gly Arg Thr Glu		
25	915	920	925
	Leu Lys Leu Glu Asp Lys His Arg Val Val Ile Gln Arg Asp Glu Gly		
	930	935	940
	His His Val Ala Tyr Thr Thr Arg Glu Val Gly Gln Tyr Leu Val Val		
	945	950	955
			960



Glu Ser Ser Thr Gly Ile Ile Val Ile Trp Asp Lys Arg Thr Thr Val  
                     965                    970                    975  
 Phe Ile Lys Leu Ala Pro Ser Tyr Lys Gly Thr Val Cys Gly Leu Cys  
                     980                    985                    990  
 5 Gly Asn Phe Asp His Arg Ser Asn Asn Asp Phe Thr Thr Arg Asp His  
                     995                    1000                    1005  
 Met Val Val Ser Ser Glu Leu Asp Phe Gly Asn Ser Trp Lys Glu Ala  
                     1010                    1015                    1020  
 Pro Thr Cys Pro Asp Val Ser Thr Asn Pro Glu Pro Cys Ser Leu Asn  
 10 1025                    1030                    1035                    1040  
 Pro His Arg Arg Ser Trp Ala Glu Lys Gln Cys Ser Ile Leu Lys Ser  
                     1045                    1050                    1055  
 Ser Val Phe Ser Ile Cys His Ser Lys Val Asp Pro Lys Pro Phe Tyr  
                     1060                    1065                    1070  
 15 Glu Ala Cys Val His Asp Ser Cys Ser Cys Asp Thr Gly Gly Asp Cys  
                     1075                    1080                    1085  
 Glu Cys Phe Cys Ser Ala Val Ala Ser Tyr Ala Gln Glu Cys Thr Lys  
                     1090                    1095                    1100  
 Glu Gly Ala Cys Val Phe Trp Arg Thr Pro Asp Leu Cys Pro Ile Phe  
 20 1105                    1110                    1115                    1120  
 Cys Asp Tyr Tyr Asn Pro Pro His Glu Cys Glu Trp His Tyr Glu Pro  
                     1125                    1130                    1135  
 Cys Gly Asn Arg Ser Phe Glu Thr Cys Arg Thr Ile Asn Gly Ile His  
                     1140                    1145                    1150  
 25 Ser Asn Ile Ser Val Ser Tyr Leu Glu Gly Cys Tyr Pro Arg Cys Pro  
                     1155                    1160                    1165  
 Lys Asp Arg Pro Ile Tyr Glu Glu Asp Leu Lys Lys Cys Val Thr Ala  
                     1170                    1175                    1180  
 Asp Lys Cys Gly Cys Tyr Val Glu Asp Thr His Tyr Pro Pro Gly Ala  
                     388

	1185	1190	1195	1200
	Ser Val Pro Thr Glu Glu Thr Cys Lys Ser Cys Val Cys Thr Asn Ser			
	1205	1210	1215	
	Ser Gln Val Val Cys Arg Pro Glu Glu Gly Lys Ile Leu Asn Gln Thr			
5	1220	1225	1230	
	Gln Asp Gly Ala Phe Cys Tyr Trp Glu Ile Cys Gly Pro Asn Gly Thr			
	1235	1240	1245	
	Val Glu Lys His Phe Asn Ile Cys Ser Ile Thr Thr Arg Pro Ser Thr			
	1250	1255	1260	
10	Leu Thr Thr Phe Thr Thr Ile Thr Leu Pro Thr Thr Pro Thr Ser Phe			
	1265	1270	1275	1280
	Thr Thr Thr Thr Thr Thr Thr Thr Pro Thr Ser Ser Thr Val Leu Ser			
	1285	1290	1295	
	Thr Thr Pro Lys Leu Cys Cys Leu Trp Ser Asp Trp Ile Asn Glu Asp			
15	1300	1305	1310	
	His Pro Ser Ser Gly Ser Asp Asp Gly Asp Arg Glu Pro Phe Asp Gly			
	1315	1320	1325	
	Val Cys Gly Ala Pro Glu Asp Ile Glu Cys Arg Ser Val Lys Asp Pro			
	1330	1335	1340	
20	His Leu Ser Leu Glu Gln His Gly Gln Lys Val Gln Cys Asp Val Ser			
	1345	1350	1355	1360
	Val Gly Phe Ile Cys Lys Asn Glu Asp Gln Phe Gly Asn Gly Pro Phe			
	1365	1370	1375	
	Gly Leu Cys Tyr Asp Tyr Lys Ile Arg Val Asn Cys Cys Trp Pro Met			
25	1380	1385	1390	
	Asp Lys Cys Ile Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ser Pro			
	1395	1400	1405	
	Pro Pro Thr Thr Thr Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro			
	1410	1415	1420	

Pro Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro  
 1425 1430 1435 1440  
 Pro Ile Thr Thr Thr Thr Thr Pro Leu Pro Thr Thr Thr Pro Ser Pro  
 1445 1450 1455  
 5 Pro Ile Ser Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro  
 1460 1465 1470  
 Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr  
 1475 1480 1485  
 Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Met  
 10 1490 1495 1500  
 Thr Thr Pro Ile Thr Pro Pro Ala Ser Thr Thr Thr Leu Pro Pro Thr  
 1505 1510 1515 1520  
 Thr Thr Pro Ser Pro Pro Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr  
 1525 1530 1535  
 15 Thr Thr Pro Ser Pro Pro Thr Thr Thr Pro Ile Thr Pro Pro Thr Ser  
 1540 1545 1550  
 Thr Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr  
 1555 1560 1565  
 Thr Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr  
 20 1570 1575 1580  
 Thr Pro Ser Pro Pro Thr Ile Thr Thr Thr Thr Pro Pro Pro Thr Thr  
 1585 1590 1595 1600  
 Thr Pro Ser Pro Pro Thr Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr  
 1605 1610 1615  
 25 Thr Pro Ser Pro Pro Thr Thr Thr Pro Ile Thr Pro Pro Thr Ser Thr  
 1620 1625 1630  
 Thr Thr Leu Pro Pro Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr Thr  
 1635 1640 1645  
 Thr Thr Pro Pro Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr  
 390

	1650	1655	1660	
	Pro Ser Pro Pro Ile Thr Thr Thr Thr Thr Pro Pro Pro Thr Thr Thr			
	1665	1670	1675	1680
	Pro Ser Ser Pro Ile Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Met			
5	1685	1690	1695	
	Thr Thr Pro Ser Pro Thr Thr Thr Pro Ser Ser Pro Ile Thr Thr Thr			
	1700	1705	1710	
	Thr Thr Pro Ser Ser Thr Thr Thr Pro Ser Pro Pro Pro Thr Thr Met			
	1715	1720	1725	
10	Thr Thr Pro Ser Pro Thr Thr Thr Pro Ser Pro Pro Thr Thr Thr Met			
	1730	1735	1740	
	Thr Thr Leu Pro Pro Thr Thr Thr Ser Ser Pro Leu Thr Thr Thr Pro			
	1745	1750	1755	1760
	Leu Pro Pro Ser Ile Thr Pro Pro Thr Phe Ser Pro Phe Ser Thr Thr			
15	1765	1770	1775	
	Thr Pro Thr Thr Pro Cys Val Pro Leu Cys Asn Trp Thr Gly Trp Leu			
	1780	1785	1790	
	Asp Ser Gly Lys Pro Asn Phe His Lys Pro Gly Gly Asp Thr Glu Leu			
	1795	1800	1805	
20	Ile Gly Asp Val Cys Gly Pro Gly Trp Ala Ala Asn Ile Ser Cys Arg			
	1810	1815	1820	
	Ala Thr Met Tyr Pro Asp Val Pro Ile Gly Gln Leu Gly Gln Thr Val			
	1825	1830	1835	1840
	Val Cys Asp Val Ser Val Gly Leu Ile Cys Lys Asn Glu Asp Gln Lys			
25	1845	1850	1855	
	Pro Gly Gly Val Ile Pro Met Ala Phe Cys Leu Asn Tyr Glu Ile Asn			
	1860	1865	1870	
	Val Gln Cys Cys Glu Cys Val Thr Gln Pro Thr Thr Met Thr Thr Thr			
	1875	1880	1885	

Thr Thr Glu Asn Pro Thr Pro Pro Thr Thr Thr Pro Ile Thr Thr Thr  
 1890 1895 1900  
 Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr  
 1905 1910 1915 1920  
 5 Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro  
 1925 1930 1935  
 Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr  
 1940 1945 1950  
 Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr  
 10 1955 1960 1965  
 Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly  
 1970 1975 1980  
 Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr  
 1985 1990 1995 2000  
 15 Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile  
 2005 2010 2015  
 Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln  
 2020 2025 2030  
 Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr  
 20 2035 2040 2045  
 Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr  
 2050 2055 2060  
 Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro  
 2065 2070 2075 2080  
 25 Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr  
 2085 2090 2095  
 Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr  
 2100 2105 2110  
 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr

	2115	2120	2125
	Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr		
	2130	2135	2140
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val		
5	2145	2150	2155
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro		2160
		2165	2170
			2175
	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr		
	2180	2185	2190
10	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro		
	2195	2200	2205
	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr		
	2210	2215	2220
	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr		
15	2225	2230	2235
			2240
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro		
	2245	2250	2255
	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr		
	2260	2265	2270
20	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr		
	2275	2280	2285
	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro		
	2290	2295	2300
	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr		
25	2305	2310	2315
			2320
	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
	2325	2330	2335
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
	2340	2345	2350

Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr  
 2355 2360 2365  
 Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile  
 2370 2375 2380  
 5 Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln  
 2385 2390 2395 2400  
 Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr  
 2405 2410 2415  
 Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr  
 10 2420 2425 2430  
 Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro  
 2435 2440 2445  
 Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr  
 2450 2455 2460  
 15 Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr  
 2465 2470 2475 2480  
 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr  
 2485 2490 2495  
 Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr  
 20 2500 2505 2510  
 Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val  
 2515 2520 2525  
 Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro  
 2530 2535 2540  
 25 Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr  
 2545 2550 2555 2560  
 Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro  
 2565 2570 2575  
 Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr

	2580	2585	2590
	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr		
	2595	2600	2605
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro		
5	2610	2615	2620
	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr		
	2625	2630	2635 2640
	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr		
	2645	2650	2655
10	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro		
	2660	2665	2670
	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr		
	2675	2680	2685
	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
15	2690	2695	2700
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
	2705	2710	2715 2720
	Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr		
	2725	2730	2735
20	Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile		
	2740	2745	2750
	Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln		
	2755	2760	2765
	Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr		
25	2770	2775	2780
	Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr		
	2785	2790	2795 2800
	Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro		
	2805	2810	2815
	395		



Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr  
 2820 2825 2830  
 Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr  
 2835 2840 2845  
 5 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr  
 2850 2855 2860  
 Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr  
 2865 2870 2875 2880  
 Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val  
 10 2885 2890 2895  
 Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro  
 2900 2905 2910  
 Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr  
 2915 2920 2925  
 15 Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro  
 2930 2935 2940  
 Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr  
 2945 2950 2955 2960  
 Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr  
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 Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro  
 2980 2985 2990  
 Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr  
 2995 3000 3005  
 25 Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr  
 3010 3015 3020  
 Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro  
 3025 3030 3035 3040  
 Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr  
 396

	3045	3050	3055
	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
	3060	3065	3070
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
5	3075	3080	3085
	Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr		
	3090	3095	3100
	Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile		
	3105	3110	3115 3120
10	Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln		
	3125	3130	3135
	Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr		
	3140	3145	3150
	Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr		
15	3155	3160	3165
	Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro		
	3170	3175	3180
	Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr		
	3185	3190	3195 3200
20	Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr		
	3205	3210	3215
	Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr		
	3220	3225	3230
	Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr		
25	3235	3240	3245
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val		
	3250	3255	3260
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro		
	3265	3270	3275 3280

	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr		
	3285	3290	3295
	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro		
	3300	3305	3310
5	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr		
	3315	3320	3325
	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr		
	3330	3335	3340
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro		
10	3345	3350	3355 3360
	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr		
	3365	3370	3375
	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr		
	3380	3385	3390
15	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro		
	3395	3400	3405
	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr		
	3410	3415	3420
	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
20	3425	3430	3435 3440
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
	3445	3450	3455
	Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr		
	3460	3465	3470
25	Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile		
	3475	3480	3485
	Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln		
	3490	3495	3500
	Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr		
	398		

	3505	3510	3515	3520
	Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr			
	3525		3530	3535
	Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro			
5	3540	3545	3550	
	Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr			
	3555	3560	3565	
	Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr			
	3570	3575	3580	
10	Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr			
	3585	3590	3595	3600
	Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr			
	3605	3610	3615	
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Val			
15	3620	3625	3630	
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro			
	3635	3640	3645	
	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr			
	3650	3655	3660	
20	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro			
	3665	3670	3675	3680
	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr			
	3685	3690	3695	
	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr			
25	3700	3705	3710	
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro			
	3715	3720	3725	
	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr			
	3730	3735	3740	

Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr  
 3745 3750 3755 3760  
 Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro  
 3765 3770 3775  
 5 Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr  
 3780 3785 3790  
 Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr  
 3795 3800 3805  
 Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly  
 10 3810 3815 3820  
 Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr  
 3825 3830 3835 3840  
 Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile  
 3845 3850 3855  
 15 Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln  
 3860 3865 3870  
 Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr  
 3875 3880 3885  
 Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr  
 20 3890 3895 3900  
 Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro  
 3905 3910 3915 3920  
 Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr  
 3925 3930 3935  
 25 Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr  
 3940 3945 3950  
 Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr  
 3955 3960 3965  
 Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr  
 400

	3970	3975	3980
	Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val		
	3985	3990	3995 4000
	Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro		
5	4005	4010	4015
	Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr		
	4020	4025	4030
	Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro		
	4035	4040	4045
10	Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr		
	4050	4055	4060
	Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr		
	4065	4070	4075 4080
	Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro		
15	4085	4090	4095
	Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr		
	4100	4105	4110
	Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr		
	4115	4120	4125
20	Thr Thr Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro		
	4130	4135	4140
	Thr Gly Thr Gln Thr Pro Thr Thr Thr Pro Ile Thr Thr Thr Thr Thr		
	4145	4150	4155 4160
	Val Thr Pro Thr Pro Thr Pro Thr Gly Thr Gln Thr Pro Thr Thr Thr		
25	4165	4170	4175
	Pro Ile Thr Thr Thr Thr Thr Val Thr Pro Thr Pro Thr Pro Thr Gly		
	4180	4185	4190
	Thr Gln Thr Gly Pro Pro Thr His Thr Ser Thr Ala Pro Ile Ala Glu		
	4195	4200	4205
		401	

Leu Thr Thr Ser Asn Pro Pro Pro Glu Ser Ser Thr Pro Gln Thr Ser  
 4210 4215 4220  
 Arg Ser Thr Ser Ser Pro Leu Thr Glu Ser Thr Thr Leu Leu Ser Thr  
 4225 4230 4235 4240  
 5 Leu Pro Pro Ala Ile Glu Met Thr Ser Thr Ala Pro Pro Ser Thr Pro  
 4245 4250 4255  
 Thr Ala Pro Thr Thr Thr Ser Gly Gly His Thr Leu Ser Pro Pro Pro  
 4260 4265 4270  
 Ser Thr Thr Thr Ser Pro Pro Gly Thr Pro Thr Arg Gly Thr Thr Thr  
 10 4275 4280 4285  
 Gly Ser Ser Ser Ala Pro Thr Pro Ser Thr Val Gln Thr Thr Thr Thr  
 4290 4295 4300  
 Ser Ala Trp Thr Pro Thr Pro Thr Pro Leu Ser Thr Pro Ser Ile Ile  
 4305 4310 4315 4320  
 15 Arg Thr Thr Gly Leu Arg Pro Tyr Pro Ser Ser Val Leu Ile Cys Cys  
 4325 4330 4335  
 Val Leu Asn Asp Thr Tyr Tyr Ala Pro Gly Glu Glu Val Tyr Asn Gly  
 4340 4345 4350  
 Thr Tyr Gly Asp Thr Cys Tyr Phe Val Asn Cys Ser Leu Ser Cys Thr  
 20 4355 4360 4365  
 Leu Glu Phe Tyr Asn Trp Ser Cys Pro Ser Thr Pro Ser Pro Thr Pro  
 4370 4375 4380  
 Thr Pro Ser Lys Ser Thr Pro Thr Pro Ser Lys Pro Ser Ser Thr Pro  
 4385 4390 4395 4400  
 25 Ser Lys Pro Thr Pro Gly Thr Lys Pro Pro Glu Cys Pro Asp Phe Asp  
 4405 4410 4415  
 Pro Pro Arg Gln Glu Asn Glu Thr Trp Trp Leu Cys Asp Cys Phe Met  
 4420 4425 4430  
 Ala Thr Cys Lys Tyr Asn Asn Thr Val Glu Ile Val Lys Val Glu Cys  
 402

	4435	4440	4445
	Glu Pro Pro Pro Met Pro Thr Cys Ser Asn Gly Leu Gln Pro Val Arg		
	4450	4455	4460
	Val Glu Asp Pro Asp Gly Cys Cys Trp His Trp Glu Cys Asp Cys Tyr		
5	4465	4470	4475 4480
	Cys Thr Gly Trp Gly Asp Pro His Tyr Val Thr Phe Asp Gly Leu Tyr		
	4485	4490	4495
	Tyr Ser Tyr Gln Gly Asn Cys Thr Tyr Val Leu Val Glu Glu Ile Ser		
	4500	4505	4510
10	Pro Ser Val Asp Asn Phe Gly Val Tyr Ile Asp Asn Tyr His Cys Asp		
	4515	4520	4525
	Pro Asn Asp Lys Val Ser Cys Pro Arg Thr Leu Ile Val Arg His Glu		
	4530	4535	4540
	Thr Gln Glu Val Leu Ile Lys Thr Val His Met Met Pro Met Gln Val		
15	4545	4550	4555 4560
	Gln Val Gln Val Asn Arg Gln Ala Val Ala Leu Pro Tyr Lys Lys Tyr		
	4565	4570	4575
	Gly Leu Glu Val Tyr Gln Ser Gly Ile Asn Tyr Val Val Asp Ile Pro		
	4580	4585	4590
20	Glu Leu Gly Val Leu Val Ser Tyr Asn Gly Leu Ser Phe Ser Val Arg		
	4595	4600	4605
	Leu Pro Tyr His Arg Phe Gly Asn Asn Thr Lys Gly Gln Cys Gly Thr		
	4610	4615	4620
	Cys Thr Asn Thr Thr Ser Asp Asp Cys Ile Leu Pro Ser Gly Glu Ile		
25	4625	4630	4635 4640
	Val Ser Asn Cys Glu Ala Ala Ala Asp Gln Trp Leu Val Asn Asp Pro		
	4645	4650	4655
	Ser Lys Pro His Cys Pro His Ser Ser Ser Thr Thr Lys Arg Pro Ala		
	4660	4665	4670
	403		



Val Thr Val Pro Gly Gly Gly Lys Thr Thr Pro His Lys Asp Cys Thr  
 4675 4680 4685  
 Pro Ser Pro Leu Cys Gln Leu Ile Lys Asp Ser Leu Phe Ala Gln Cys  
 4690 4695 4700  
 5 His Ala Leu Val Pro Pro Gln His Tyr Tyr Asp Ala Cys Val Phe Asp  
 4705 4710 4715 4720  
 Ser Cys Phe Met Pro Gly Ser Ser Leu Glu Cys Ala Ser Leu Gln Ala  
 4725 4730 4735  
 Tyr Ala Ala Leu Cys Ala Gln Gln Asn Ile Cys Leu Asp Trp Arg Asn  
 10 4740 4745 4750  
 His Thr His Gly Ala Cys Leu Val Glu Cys Pro Ser His Arg Glu Tyr  
 4755 4760 4765  
 Gln Ala Cys Gly Pro Ala Glu Glu Pro Thr Cys Lys Ser Ser Ser Ser  
 4770 4775 4780  
 15 Gln Gln Asn Asn Thr Val Leu Val Glu Gly Cys Phe Cys Pro Glu Gly  
 4785 4790 4795 4800  
 Thr Met Asn Tyr Ala Pro Gly Phe Asp Val Cys Val Lys Thr Cys Gly  
 4805 4810 4815  
 Cys Val Gly Pro Asp Asn Val Pro Arg Glu Phe Gly Glu His Phe Glu  
 20 4820 4825 4830  
 Phe Asp Cys Lys Asn Cys Val Cys Leu Glu Gly Gly Ser Gly Ile Ile  
 4835 4840 4845  
 Cys Gln Pro Lys Arg Cys Ser Gln Lys Pro Val Thr His Cys Val Glu  
 4850 4855 4860  
 25 Asp Gly Thr Tyr Leu Ala Thr Glu Val Asn Pro Ala Asp Thr Cys Cys  
 4865 4870 4875 4880  
 Asn Ile Thr Val Cys Lys Cys Asn Thr Ser Leu Cys Lys Glu Lys Pro  
 4885 4890 4895  
 Ser Val Cys Pro Leu Gly Phe Glu Val Lys Ser Lys Met Val Pro Gly

	4900	4905	4910
	Arg Cys Cys Pro Phe Tyr Trp Cys Glu Ser Lys Gly Val Cys Val His		
	4915	4920	4925
	Gly Asn Ala Glu Tyr Gln Pro Gly Ser Pro Val Tyr Ser Ser Lys Cys		
5	4930	4935	4940
	Gln Asp Cys Val Cys Thr Asp Lys Val Asp Asn Asn Thr Leu Leu Asn		
	4945	4950	4955
	Val Ile Ala Cys Thr His Val Pro Cys Asn Thr Ser Cys Ser Pro Gly		
	4965	4970	4975
10	Phe Glu Leu Met Glu Ala Pro Gly Glu Cys Cys Lys Lys Cys Glu Gln		
	4980	4985	4990
	Thr His Cys Ile Ile Lys Arg Pro Asp Asn Gln His Val Ile Leu Lys		
	4995	5000	5005
	Pro Gly Asp Phe Lys Ser Asp Pro Lys Asn Asn Cys Thr Phe Phe Ser		
15	5010	5015	5020
	Cys Val Lys Ile His Asn Gln Leu Ile Ser Ser Val Ser Asn Ile Thr		
	5025	5030	5035
	Cys Pro Asn Phe Asp Ala Ser Ile Cys Ile Pro Gly Ser Ile Thr Phe		
	5045	5050	5055
20	Met Pro Asn Gly Cys Cys Lys Thr Cys Thr Pro Arg Asn Glu Thr Arg		
	5060	5065	5070
	Val Pro Cys Ser Thr Val Pro Val Thr Thr Glu Val Ser Tyr Ala Gly		
	5075	5080	5085
	Cys Thr Lys Thr Val Leu Met Asn His Cys Ser Gly Ser Cys Gly Thr		
25	5090	5095	5100
	Phe Val Met Tyr Ser Ala Lys Ala Gln Ala Leu Asp His Ser Cys Ser		
	5105	5110	5115
	Cys Cys Lys Glu Glu Lys Thr Ser Gln Arg Glu Val Val Leu Ser Cys		
	5125	5130	5135
	405		

Pro Asn Gly Gly Ser Leu Thr His Thr Tyr Thr His Ile Glu Ser Cys

5140

5145

5150

Gln Cys Gln Asp Thr Val Cys Gly Leu Pro Thr Gly Thr Ser Arg Arg

5155

5160

5165

5 Ala Arg Arg Ser Pro Arg His Leu Gly Ser Gly

5170

5175

10

<210> 122

<211> 1217

<212> PRT

<213> Homo sapiens

15

<400> 122

Ile Thr Ile Thr Glu Thr Thr Ser His Ser Thr Pro Ser Tyr Thr Thr

1

5

10

15

Ser Ile Thr Thr Thr Glu Thr Pro Ser His Ser Thr Pro Ser Tyr Thr

20

20

25

30

Thr Ser Ile Thr Thr Thr Glu Thr Pro Ser His Ser Thr Pro Ser Phe

35

40

45

Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser His Ser Thr Pro Ser

50

55

60

25 Phe Thr Ser Ser Ile Arg Thr Thr Glu Thr Thr Ser Tyr Ser Thr Pro

65

70

75

80

Ser Phe Thr Ser Ser Asn Thr Ile Thr Glu Thr Thr Ser His Ser Thr

85

90

95

Pro Ser Tyr Ile Thr Ser Ile Thr Thr Glu Thr Pro Ser Ser Ser

406

	100	105	110
	Thr Pro Ser Phe Ser Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser His		
	115	120	125
	Ser Thr Pro Gly Phe Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser		
5	130	135	140
	His Ser Thr Pro Ser Phe Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr		
	145	150	155
	Ser His Asp Thr Pro Ser Phe Thr Ser Ser Ile Thr Thr Ser Glu Thr		160
	165	170	175
10	Pro Ser His Ser Thr Pro Ser Ser Thr Ser Leu Ile Thr Thr Thr Lys		
	180	185	190
	Thr Thr Ser His Ser Thr Pro Ser Phe Thr Ser Ser Ile Thr Thr Thr		
	195	200	205
	Glu Thr Thr Ser His Ser Ala Arg Ser Phe Thr Ser Ser Ile Thr Thr		
15	210	215	220
	Thr Glu Thr Thr Ser His Asn Thr Arg Ser Phe Thr Ser Ser Ile Thr		
	225	230	235
	Thr Thr Glu Thr Asn Ser His Ser Thr Thr Ser Phe Thr Ser Ser Ile		240
	245	250	255
20	Thr Thr Thr Glu Thr Thr Ser His Ser Thr Pro Ser Phe Ser Ser Ser		
	260	265	270
	Ile Thr Thr Thr Glu Thr Pro Leu His Ser Thr Pro Gly Leu Thr Ser		
	275	280	285
	Trp Val Thr Thr Thr Lys Thr Thr Ser His Ile Thr Pro Gly Leu Thr		
25	290	295	300
	Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser His Ser Thr Pro Gly Phe		
	305	310	315
	Thr Ser Ser Ile Thr Thr Thr Glu Thr Thr Ser Glu Ser Thr Pro Ser		320
	325	330	335

Leu Ser Ser Ser Thr Ile Tyr Ser Thr Val Ser Thr Ser Thr Thr Ala  
 340 345 350  
 Ile Thr Ser His Phe Thr Thr Ser Glu Thr Ala Val Thr Pro Thr Pro  
 355 360 365  
 5 Val Thr Pro Ser Ser Leu Ser Thr Asp Ile Pro Thr Thr Ser Leu Arg  
 370 375 380  
 Thr Leu Thr Pro Ser Ser Val Gly Thr Ser Thr Ser Leu Thr Thr Thr  
 385 390 395 400  
 Thr Asp Phe Pro Ser Ile Pro Thr Asp Ile Ser Thr Leu Pro Thr Arg  
 10 405 410 415  
 Thr His Ile Ile Ser Ser Ser Pro Ser Ile Gln Ser Thr Glu Thr Ser  
 420 425 430  
 Ser Leu Val Gly Thr Thr Ser Pro Thr Met Ser Thr Val Arg Met Thr  
 435 440 445  
 15 Leu Arg Ile Thr Glu Asn Thr Pro Ile Ser Ser Phe Ser Thr Ser Ile  
 450 455 460  
 Val Val Ile Pro Glu Thr Pro Thr Gln Thr Pro Pro Val Leu Thr Ser  
 465 470 475 480  
 Ala Thr Gly Thr Gln Thr Ser Pro Ala Pro Thr Thr Val Thr Phe Gly  
 20 485 490 495  
 Ser Thr Asp Ser Ser Thr Ser Thr Leu His Thr Leu Thr Pro Ser Thr  
 500 505 510  
 Ala Leu Ser Thr Ile Val Ser Thr Ser Gln Val Pro Ile Pro Ser Thr  
 515 520 525  
 25 His Ser Ser Thr Leu Gln Thr Thr Pro Ser Thr Pro Ser Leu Gln Thr  
 530 535 540  
 Ser Leu Thr Ser Thr Ser Glu Phe Thr Thr Glu Ser Phe Thr Arg Gly  
 545 550 555 560  
 Ser Thr Ser Thr Asn Ala Ile Leu Thr Ser Phe Ser Thr Ile Ile Trp  
 408

	565	570	575
	Ser Ser Thr Pro Thr Ile Ile Met Ser Ser Ser Pro Ser Ser Ala Ser		
	580	585	590
	Ile Thr Pro Val Phe Ser Thr Thr Ile His Ser Val Pro Ser Ser Pro		
5	595	600	605
	Tyr Ile Phe Ser Thr Glu Asn Val Gly Ser Ala Ser Ile Thr Gly Phe		
	610	615	620
	Pro Ser Leu Ser Ser Ser Ala Thr Thr Ser Thr Ser Ser Thr Ser Ser		
	625	630	635 640
10	Ser Leu Thr Thr Ala Leu Thr Glu Ile Thr Pro Phe Ser Tyr Ile Ser		
	645	650	655
	Leu Pro Ser Thr Thr Pro Cys Pro Gly Thr Ile Thr Ile Thr Ile Val		
	660	665	670
	Pro Ala Ser Pro Thr Asp Pro Cys Val Glu Met Asp Pro Ser Thr Glu		
15	675	680	685
	Ala Thr Ser Pro Pro Thr Thr Pro Leu Thr Val Phe Pro Phe Thr Thr		
	690	695	700
	Glu Met Val Thr Cys Pro Thr Ser Ile Ser Ile Gln Thr Thr Leu Thr		
	705	710	715 720
20	Thr Tyr Met Asp Thr Ser Ser Met Met Pro Glu Ser Glu Ser Ser Ile		
	725	730	735
	Ser Pro Asn Ala Ser Ser Ser Thr Gly Thr Gly Thr Val Pro Thr Asn		
	740	745	750
	Thr Val Phe Thr Ser Thr Arg Leu Pro Thr Ser Glu Thr Trp Leu Ser		
25	755	760	765
	Asn Ser Ser Val Ile Pro Leu Pro Leu Pro Gly Val Ser Thr Ile Pro		
	770	775	780
	Leu Thr Met Lys Pro Ser Ser Ser Leu Pro Thr Ile Leu Arg Thr Ser		
	785	790	795 800

Ser Lys Ser Thr His Pro Ser Pro Pro Thr Thr Arg Thr Ser Glu Thr  
 805 810 815  
 Pro Val Ala Thr Thr Gln Thr Pro Thr Thr Leu Thr Ser Arg Arg Thr  
 820 825 830  
 5 Thr Arg Ile Thr Ser Gln Met Thr Thr Gln Ser Thr Leu Thr Thr Thr  
 835 840 845  
 Ala Gly Thr Cys Asp Asn Gly Gly Thr Trp Glu Gln Gly Gln Cys Ala  
 850 855 860  
 Cys Leu Pro Gly Phe Ser Gly Asp Arg Cys Gln Leu Gln Thr Arg Cys  
 10 865 870 875 880  
 Gln Asn Gly Gly Gln Trp Asp Gly Leu Lys Cys Gln Cys Pro Ser Thr  
 885 890 895  
 Phe Tyr Gly Ser Ser Cys Glu Phe Ala Val Glu Gln Val Asp Leu Asp  
 900 905 910  
 15 Val Val Glu Thr Glu Val Gly Met Glu Val Ser Val Asp Gln Gln Phe  
 915 920 925  
 Ser Pro Asp Leu Asn Asp Asn Thr Ser Gln Ala Tyr Arg Asp Phe Asn  
 930 935 940  
 Lys Thr Phe Trp Asn Gln Met Gln Lys Ile Phe Ala Asp Met Gln Gly  
 20 945 950 955 960  
 Phe Thr Phe Lys Gly Val Glu Ile Leu Ser Leu Arg Asn Gly Ser Ile  
 965 970 975  
 Val Val Asp Tyr Leu Val Leu Leu Glu Met Pro Phe Ser Pro Gln Leu  
 980 985 990  
 25 Glu Ser Glu Tyr Glu Gln Val Lys Thr Thr Leu Lys Glu Gly Leu Gln  
 995 1000 1005  
 Asn Ala Ser Gln Asp Val Asn Ser Cys Gln Asp Ser Gln Thr Leu Cys  
 1010 1015 1020  
 Phe Lys Pro Asp Ser Ile Lys Val Asn Asn Asn Ser Lys Thr Glu Leu

	1025	1030	1035	1040
	Thr Pro Ala Ala Ile Cys Arg Arg Ala Ala Pro Thr Gly Tyr Glu Glu			
	1045	1050	1055	
	Phe Tyr Phe Pro Leu Val Glu Ala Thr Arg Leu Arg Cys Val Thr Lys			
5	1060	1065	1070	
	Cys Thr Ser Gly Val Asp Asn Ala Ile Asp Cys His Gln Gly Gln Cys			
	1075	1080	1085	
	Val Leu Glu Thr Ser Gly Pro Thr Cys Arg Cys Tyr Ser Thr Asp Thr			
	1090	1095	1100	
10	His Trp Phe Ser Gly Pro Arg Cys Glu Val Ala Val His Trp Arg Ala			
	1105	1110	1115	1120
	Leu Val Gly Gly Leu Thr Ala Gly Ala Ala Leu Leu Val Leu Leu Leu			
	1125	1130	1135	
	Leu Ala Leu Gly Val Arg Ala Val Arg Ser Gly Trp Trp Gly Gly Gln			
15	1140	1145	1150	
	Arg Arg Gly Arg Ser Trp Asp Gln Asp Arg Lys Trp Phe Glu Thr Trp			
	1155	1160	1165	
	Asp Glu Glu Val Val Gly Thr Phe Ser Asn Trp Gly Phe Glu Asp Asp			
	1170	1175	1180	
20	Gly Thr Asp Lys Asp Thr Asn Phe Tyr Val Ala Leu Glu Asn Val Asp			
	1185	1190	1195	1200
	Thr Thr Met Lys Val His Ile Lys Arg Pro Glu Met Thr Ser Ser Ser			
	1205	1210	1215	
	Val			

25

<210> 123

<211> 1373



<212> PRT

<213> Homo sapiens

<400> 123

5 Met Ser Val Gly Arg Arg Lys Leu Ala Leu Leu Trp Ala Leu Ala Leu  
1 5 10 15  
Ala Leu Ala Cys Thr Arg His Thr Gly His Ala Gln Asp Gly Ser Ser  
20 25 30  
Glu Ser Ser Tyr Lys His His Pro Ala Leu Ser Pro Ile Ala Arg Gly  
10 35 40 45  
Pro Ile Gly Val Pro Leu Arg Gly Ala Thr Val Phe Pro Ser Leu Arg  
50 55 60  
Thr Ile Pro Val Val Arg Ala Ser Asn Pro Ala His Asn Gly Arg Val  
65 70 75 80  
15 Cys Ser Thr Trp Gly Ser Phe His Tyr Lys Thr Phe Asp Gly Asp Val  
85 90 95  
Phe Arg Phe Pro Gly Leu Cys Asn Tyr Val Phe Ser Glu His Cys Gly  
100 105 110  
Ala Ala Tyr Glu Asp Phe Asn Ile Pro Ala Thr Pro Gln Pro Gly Val  
20 115 120 125  
Ser Gly Pro His Ala Glu Gln Gly Pro His Glu Gly Gly Trp Arg Gly  
130 135 140  
His Pro Ala Asp Gln Gly Leu Arg Pro Gly Gln Arg Pro Pro Gly Pro  
145 150 155 160  
25 Ala Ala Leu Gln Pro Val Trp Gly Pro His Ser Ala Arg Ala Ala Ala  
165 170 175  
Thr Pro Arg Trp Lys Pro Gly Trp Ala Leu Ser Ser Cys Gly Thr Thr  
180 185 190  
Met Thr Ala Cys Cys Trp Lys Leu Asp Thr Lys Tyr Ala Asn Lys Asn

	195	200	205
	Leu Trp Ala Leu Trp Gly Leu Gln Arg Asp Ala Arg Gly Gln Arg Ala		
	210	215	220
	Pro Leu Pro Gln His Gln Ala Asp Thr His Gly Ile Arg Glu Pro Ala		
5	225	230	235 240
	Glu Arg Trp Thr Asn Pro Arg Ser Ser Val Arg Thr Leu Ser Leu Asn		
	245	250	255
	Pro Arg Arg Thr Ala Pro Leu Ala Leu Ala Ser Cys Glu Glu Leu Leu		
	260	265	270
10	His Gly Gln Leu Phe Ser Gly Cys Val Ala Leu Val Asp Val Gly Ser		
	275	280	285
	Tyr Leu Glu Ala Cys Arg Gln Asp Leu Cys Phe Cys Glu Asp Thr Asp		
	290	295	300
	Leu Leu Ser Cys Val Cys His Thr Leu Ala Glu Tyr Ser Arg Gln Cys		
15	305	310	315 320
	Thr His Ala Gly Gly Leu Pro Gln Asp Trp Arg Gly Pro Asp Phe Cys		
	325	330	335
	Pro Gln Lys Cys Pro Asn Asn Met Gln Tyr His Glu Cys Arg Ser Pro		
	340	345	350
20	Cys Ala Asp Thr Cys Ser Asn Gln Glu His Ser Arg Ala Cys Glu Asp		
	355	360	365
	His Cys Val Ala Gly Cys Phe Cys Pro Glu Gly Thr Val Leu Asp Asp		
	370	375	380
	Ile Gly Gln Thr Gly Cys Val Pro Val Ser Lys Cys Ala Cys Val Tyr		
25	385	390	395 400
	Asn Gly Ala Ala Tyr Ala Pro Gly Ala Thr Tyr Ser Thr Asp Cys Thr		
	405	410	415
	Asn Cys Thr Cys Ser Gly Gly Arg Trp Ser Cys Gln Glu Val Pro Cys		
	420	425	430
		413	

Pro Gly Thr Cys Ser Val Leu Gly Gly Ala His Phe Ser Thr Phe Asp  
 435 440 445  
 Gly Lys Gln Tyr Thr Val His Gly Asp Cys Ser Tyr Val Leu Thr Lys  
 450 455 460  
 5 Pro Cys Asp Ser Ser Ala Phe Thr Val Leu Ala Glu Leu Arg Arg Cys  
 465 470 475 480  
 Gly Leu Thr Asp Ser Glu Thr Cys Leu Lys Ser Val Thr Leu Ser Leu  
 485 490 495  
 Asp Gly Ala Gln Thr Val Val Val Ile Lys Ala Ser Gly Glu Val Phe  
 10 500 505 510  
 Leu Asn Gln Ile Tyr Thr Gln Leu Pro Ile Ser Ala Ala Asn Val Thr  
 515 520 525  
 Ile Phe Arg Pro Ser Thr Phe Phe Ile Ile Ala Gln Thr Ser Leu Gly  
 530 535 540  
 15 Leu Gln Leu Asn Leu Gln Leu Val Pro Thr Met Gln Leu Phe Met Gln  
 545 550 555 560  
 Leu Ala Pro Lys Leu Arg Gly Gln Thr Cys Gly Leu Cys Gly Asn Phe  
 565 570 575  
 Asn Ser Ile Gln Ala Asp Asp Phe Arg Thr Leu Ser Gly Val Val Glu  
 20 580 585 590  
 Ala Thr Ala Ala Ala Phe Phe Asn Thr Phe Lys Thr Gln Ala Ala Cys  
 595 600 605  
 Pro Asn Ile Arg Asn Ser Phe Glu Asp Pro Cys Ser Leu Ser Val Glu  
 610 615 620  
 25 Asn Glu Lys Tyr Ala Gln His Trp Cys Ser Gln Leu Thr Asp Ala Asp  
 625 630 635 640  
 Gly Pro Phe Gly Arg Cys His Ala Ala Val Lys Pro Gly Thr Tyr Tyr  
 645 650 655  
 Ser Asn Cys Met Phe Asp Thr Cys Asn Cys Glu Arg Ser Glu Asp Cys  
 414

	660	665	670
	Leu Cys Ala Ala Leu Ser Ser Tyr Val His Ala Cys Ala Ala Lys Gly		
	675	680	685
	Val Gln Leu Gly Gly Trp Arg Asp Gly Val Cys Thr Lys Pro Met Thr		
5	690	695	700
	Thr Cys Pro Lys Ser Met Thr Tyr His Tyr His Val Ser Thr Cys Gln		
	705	710	715
	Pro Thr Cys Arg Ser Leu Ser Glu Gly Asp Ile Thr Cys Ser Val Gly		
	725	730	735
10	Phe Ile Pro Val Asp Gly Cys Ile Cys Pro Lys Gly Thr Phe Leu Asp		
	740	745	750
	Asp Thr Gly Lys Cys Val Gln Ala Ser Asn Cys Pro Cys Tyr His Arg		
	755	760	765
	Gly Ser Met Ile Pro Asn Gly Glu Ser Val His Asp Ser Gly Ala Ile		
15	770	775	780
	Cys Thr Cys Thr His Gly Lys Leu Ser Cys Ile Gly Gly Gln Ala Pro		
	785	790	795
	Ala Pro Val Cys Ala Ala Pro Met Val Phe Phe Asp Cys Arg Asn Ala		
	805	810	815
20	Thr Pro Gly Asp Thr Gly Ala Gly Cys Gln Lys Ser Cys His Thr Leu		
	820	825	830
	Asp Met Thr Cys Tyr Ser Pro Gln Cys Val Pro Gly Cys Val Cys Pro		
	835	840	845
	Asp Gly Leu Val Ala Asp Gly Glu Gly Gly Cys Ile Thr Ala Glu Asp		
25	850	855	860
	Cys Pro Cys Val His Asn Glu Ala Ser Tyr Arg Ala Gly Gln Thr Ile		
	865	870	875
	Arg Val Gly Cys Asn Thr Cys Thr Cys Asp Ser Arg Met Trp Arg Cys		
	885	890	895

Thr Asp Asp Pro Cys Leu Ala Thr Cys Ala Val Tyr Gly Asp Gly His  
 900 905 910  
 Tyr Leu Thr Phe Asp Gly Gln Ser Tyr Ser Phe Asn Glu Glu Thr Ala  
 915 920 925  
 5 Ser Thr Arg Trp Cys Arg Thr Ala Val Ala Gly Lys Thr Ala Pro Arg  
 930 935 940  
 Thr Pro Phe Val Leu Ser Pro Arg Thr Ser Pro Ala Ala Pro Gln Gly  
 945 950 955 960  
 Pro Pro Ala Pro Arg Pro Ser Arg Phe Ser Trp Gly Asn Phe Glu Leu  
 10 965 970 975  
 Lys Leu Ser His Gly Lys Val Glu Val Ile Gly Thr Asp Glu Ser Gln  
 980 985 990  
 Glu Val Pro Tyr Thr Ile Arg Gln Met Gly Ile Tyr Leu Val Val Asp  
 995 1000 1005  
 15 Thr Asp Ile Gly Leu Val Leu Leu Trp Asp Lys Lys Thr Ser Ile Phe  
 1010 1015 1020  
 Ile Asn Leu Ser Pro Glu Phe Lys Gly Arg Val Cys Gly Leu Cys Gly  
 1025 1030 1035 1040  
 Asn Phe Asp Asp Ile Ala Val Asn Asp Phe Ala Thr Arg Ser Arg Ser  
 20 1045 1050 1055  
 Val Val Gly Asp Val Leu Glu Phe Gly Asn Ser Trp Lys Leu Ser Pro  
 1060 1065 1070  
 Ser Cys Pro Asp Ala Leu Ala Pro Lys Asp Pro Cys Thr Ala Asn Pro  
 1075 1080 1085  
 25 Phe Arg Lys Ser Trp Ala Gln Lys Gln Cys Ser Ile Leu His Gly Pro  
 1090 1095 1100  
 Thr Phe Ala Ala Cys His Ala His Val Glu Pro Ala Arg Tyr Tyr Glu  
 1105 1110 1115 1120  
 Ala Cys Val Asn Asp Ala Cys Ala Cys Asp Ser Gly Gly Asp Cys Glu

	1125	1130	1135
	Cys Phe Cys Thr Ala Val Ala Arg Tyr Ala Gln Ala Cys His Glu Val		
	1140	1145	1150
	Gly Thr Cys Val Cys Leu Arg Thr Pro Ser Ile Cys Pro Leu Phe Cys		
5	1155	1160	1165
	Asp Tyr Tyr Asn Pro Glu Gly Gln Cys Glu Trp His Tyr Gln Pro Cys		
	1170	1175	1180
	Gly Val Pro Cys Leu Arg Thr Cys Arg Asn Pro Arg Gly Asp Cys Leu		
	1185	1190	1195
			1200
10	Arg Asp Val Arg Gly Leu Glu Gly Cys Tyr Pro Lys Cys Pro Pro Glu		
	1205	1210	1215
	Ala Pro Ile Phe Asp Glu Asp Lys Met Gln Cys Val Ala Thr Cys Pro		
	1220	1225	1230
	Thr Pro Pro Leu Pro Pro Arg Cys His Val His Gly Lys Ser Tyr Arg		
15	1235	1240	1245
	Pro Gly Ala Val Val Pro Ser Asp Lys Asn Cys Gln Ser Cys Leu Cys		
	1250	1255	1260
	Thr Glu Arg Gly Val Glu Cys Thr Tyr Lys Ala Glu Ala Cys Val Cys		
	1265	1270	1275
			1280
20	Thr Tyr Asn Gly Gln Arg Phe His Pro Gly Asp Val Ile Tyr His Thr		
	1285	1290	1295
	Thr Asp Gly Thr Gly Gly Cys Ile Ser Ala Arg Cys Gly Ala Asn Gly		
	1300	1305	1310
	Thr Ile Glu Arg Arg Val Tyr Pro Cys Ser Pro Thr Thr Pro Val Pro		
25	1315	1320	1325
	Pro Thr Thr Phe Ser Phe Ser Thr Pro Pro Leu Val Val Ser Ser Thr		
	1330	1335	1340
	His Thr Pro Ser Asn Gly Pro Ser Ser Ala His Thr Gly Pro Pro Ser		
	1345	1350	1355
			1360

Ser Ala Trp Pro Thr Thr Ala Gly Thr Ser Pro Arg Thr

1365

1370

5 <210> 124

<211> 165

<212> PRT

<213> Homo sapiens

10 <400> 124

Met Glu Met Phe Gln Gly Leu Leu Leu Leu Leu Leu Ser Met Gly

1

5

10

15

Gly Thr Trp Ala Ser Lys Glu Pro Leu Arg Pro Arg Cys Arg Pro Ile

20

25

30

15 Asn Ala Thr Leu Ala Val Glu Lys Glu Gly Cys Pro Val Cys Ile Thr

35

40

45

Val Asn Thr Thr Ile Cys Ala Gly Tyr Cys Pro Thr Met Thr Arg Val

50

55

60

Leu Gln Gly Val Leu Pro Ala Leu Pro Gln Val Val Cys Asn Tyr Arg

20

65

70

75

80

Asp Val Arg Phe Glu Ser Ile Arg Leu Pro Gly Cys Pro Arg Gly Val

85

90

95

Asn Pro Val Val Ser Tyr Ala Val Ala Leu Ser Cys Gln Cys Ala Leu

100

105

110

25 Cys Arg Arg Ser Thr Thr Asp Cys Gly Gly Pro Lys Asp His Pro Leu

115

120

125

Thr Cys Asp Asp Pro Arg Phe Gln Asp Ser Ser Ser Ser Lys Ala Pro

130

135

140

Pro Pro Ser Leu Pro Ser Pro Ser Arg Leu Pro Gly Pro Ser Asp Thr

418

145                      150                      155                      160  
Pro Ile Leu Pro Gln  
165

5

<210> 125  
<211> 1210  
<212> PRT  
<213> Homo sapiens

10

<400> 125  
Met Arg Pro Ser Gly Thr Ala Gly Ala Ala Leu Leu Ala Leu Leu Ala  
1                      5                      10                      15  
Ala Leu Cys Pro Ala Ser Arg Ala Leu Glu Glu Lys Lys Val Cys Gln

15

20                      25                      30  
Gly Thr Ser Asn Lys Leu Thr Gln Leu Gly Thr Phe Glu Asp His Phe  
35                      40                      45  
Leu Ser Leu Gln Arg Met Phe Asn Asn Cys Glu Val Val Leu Gly Asn

20

Leu Glu Ile Thr Tyr Val Gln Arg Asn Tyr Asp Leu Ser Phe Leu Lys  
65                      70                      75                      80  
Thr Ile Gln Glu Val Ala Gly Tyr Val Leu Ile Ala Leu Asn Thr Val  
85                      90                      95

25

Glu Arg Ile Pro Leu Glu Asn Leu Gln Ile Ile Arg Gly Asn Met Tyr  
100                      105                      110  
Tyr Glu Asn Ser Tyr Ala Leu Ala Val Leu Ser Asn Tyr Asp Ala Asn  
115                      120                      125  
Lys Thr Gly Leu Lys Glu Leu Pro Met Arg Asn Leu Gln Glu Ile Leu

130                      135                      140



His Gly Ala Val Arg Phe Ser Asn Asn Pro Ala Leu Cys Asn Val Glu  
 145                      150                      155                      160  
 Ser Ile Gln Trp Arg Asp Ile Val Ser Ser Asp Phe Leu Ser Asn Met  
                          165                      170                      175  
 5 Ser Met Asp Phe Gln Asn His Leu Gly Ser Cys Gln Lys Cys Asp Pro  
                          180                      185                      190  
 Ser Cys Pro Asn Gly Ser Cys Trp Gly Ala Gly Glu Glu Asn Cys Gln  
                          195                      200                      205  
 Lys Leu Thr Lys Ile Ile Cys Ala Gln Gln Cys Ser Gly Arg Cys Arg  
 10           210                      215                      220  
 Gly Lys Ser Pro Ser Asp Cys Cys His Asn Gln Cys Ala Ala Gly Cys  
                          225                      230                      235                      240  
 Thr Gly Pro Arg Glu Ser Asp Cys Leu Val Cys Arg Lys Phe Arg Asp  
                          245                      250                      255  
 15 Glu Ala Thr Cys Lys Asp Thr Cys Pro Pro Leu Met Leu Tyr Asn Pro  
                          260                      265                      270  
 Thr Thr Tyr Gln Met Asp Val Asn Pro Glu Gly Lys Tyr Ser Phe Gly  
                          275                      280                      285  
 Ala Thr Cys Val Lys Lys Cys Pro Arg Asn Tyr Val Val Thr Asp His  
 20           290                      295                      300  
 Gly Ser Cys Val Arg Ala Cys Gly Ala Asp Ser Tyr Glu Met Glu Glu  
                          305                      310                      315                      320  
 Asp Gly Val Arg Lys Cys Lys Lys Cys Glu Gly Pro Cys Arg Lys Val  
                          325                      330                      335  
 25 Cys Asn Gly Ile Gly Ile Gly Glu Phe Lys Asp Ser Leu Ser Ile Asn  
                          340                      345                      350  
 Ala Thr Asn Ile Lys His Phe Lys Asn Cys Thr Ser Ile Ser Gly Asp  
                          355                      360                      365  
 Leu His Ile Leu Pro Val Ala Phe Arg Gly Asp Ser Phe Thr His Thr  
    420

	370	375	380	
	Pro	Pro	Leu	Asp
	Pro	Gln	Glu	Leu
	Asp	Pro	Ile	Leu
	Lys	Thr	Val	Lys
	Glu			
	385	390	395	400
	Ile	Thr	Gly	Phe
	Leu	Leu	Ile	Gln
	Ala	Trp	Pro	Glu
	Asn	Arg	Thr	Asp
5	405	410	415	
	Leu	His	Ala	Phe
	Glu	Asn	Leu	Glu
	Ile	Ile	Arg	Gly
	Arg	Thr	Lys	Gln
	420	425	430	
	His	Gly	Gln	Phe
	Ser	Leu	Ala	Val
	Val	Ser	Leu	Asn
	Ile	Thr	Ser	Leu
	435	440	445	
10	Gly	Leu	Arg	Ser
	Leu	Lys	Glu	Ile
	Ser	Asp	Gly	Asp
	Val	Ile	Ile	Ser
	450	455	460	
	Gly	Asn	Lys	Asn
	Leu	Cys	Tyr	Ala
	Asn	Thr	Ile	Asn
	Trp	Lys	Lys	Leu
	465	470	475	480
	Phe	Gly	Thr	Ser
	Gly	Gln	Lys	Thr
	Lys	Ile	Ile	Ser
	Asn	Arg	Gly	Glu
15	485	490	495	
	Asn	Ser	Cys	Lys
	Ala	Thr	Gly	Gln
	Val	Cys	His	Ala
	Leu	Cys	Ser	Pro
	500	505	510	
	Glu	Gly	Cys	Trp
	Gly	Pro	Glu	Pro
	Arg	Asp	Cys	Val
	Ser	Cys	Arg	Asn
	515	520	525	
20	Val	Ser	Arg	Gly
	Arg	Glu	Cys	Val
	Asp	Lys	Cys	Lys
	Leu	Leu	Glu	Gly
	530	535	540	
	Glu	Pro	Arg	Glu
	Phe	Val	Glu	Asn
	Ser	Glu	Cys	Ile
	Gln	Cys	His	Pro
	545	550	555	560
	Glu	Cys	Leu	Pro
	Gln	Ala	Met	Asn
	Ile	Thr	Cys	Thr
	Gly	Arg	Gly	Pro
25	565	570	575	
	Asp	Asn	Cys	Ile
	Gln	Cys	Ala	His
	Tyr	Ile	Asp	Gly
	Pro	His	Cys	Val
	580	585	590	
	Lys	Thr	Cys	Pro
	Ala	Gly	Val	Met
	Gly	Glu	Asn	Asn
	Thr	Leu	Val	Trp
	595	600	605	

Lys Tyr Ala Asp Ala Gly His Val Cys His Leu Cys His Pro Asn Cys  
 610 615 620  
 Thr Tyr Gly Cys Thr Gly Pro Gly Leu Glu Gly Cys Pro Thr Asn Gly  
 625 630 635 640  
 5 Pro Lys Ile Pro Ser Ile Ala Thr Gly Met Val Gly Ala Leu Leu Leu  
 645 650 655  
 Leu Leu Val Val Ala Leu Gly Ile Gly Leu Phe Met Arg Arg Arg His  
 660 665 670  
 Ile Val Arg Lys Arg Thr Leu Arg Arg Leu Leu Gln Glu Arg Glu Leu  
 10 675 680 685  
 Val Glu Pro Leu Thr Pro Ser Gly Glu Ala Pro Asn Gln Ala Leu Leu  
 690 695 700  
 Arg Ile Leu Lys Glu Thr Glu Phe Lys Lys Ile Lys Val Leu Gly Ser  
 705 710 715 720  
 15 Gly Ala Phe Gly Thr Val Tyr Lys Gly Leu Trp Ile Pro Glu Gly Glu  
 725 730 735  
 Lys Val Lys Ile Pro Val Ala Ile Lys Glu Leu Arg Glu Ala Thr Ser  
 740 745 750  
 Pro Lys Ala Asn Lys Glu Ile Leu Asp Glu Ala Tyr Val Met Ala Ser  
 20 755 760 765  
 Val Asp Asn Pro His Val Cys Arg Leu Leu Gly Ile Cys Leu Thr Ser  
 770 775 780  
 Thr Val Gln Leu Ile Thr Gln Leu Met Pro Phe Gly Cys Leu Leu Asp  
 785 790 795 800  
 25 Tyr Val Arg Glu His Lys Asp Asn Ile Gly Ser Gln Tyr Leu Leu Asn  
 805 810 815  
 Trp Cys Val Gln Ile Ala Lys Gly Met Asn Tyr Leu Glu Asp Arg Arg  
 820 825 830  
 Leu Val His Arg Asp Leu Ala Ala Arg Asn Val Leu Val Lys Thr Pro  
 422

	835	840	845
	Gln His Val Lys Ile Thr Asp Phe Gly Leu Ala Lys Leu Leu Gly Ala		
	850	855	860
	Glu Glu Lys Glu Tyr His Ala Glu Gly Gly Lys Val Pro Ile Lys Trp		
5	865	870	875 880
	Met Ala Leu Glu Ser Ile Leu His Arg Ile Tyr Thr His Gln Ser Asp		
	885	890	895
	Val Trp Ser Tyr Gly Val Thr Val Trp Glu Leu Met Thr Phe Gly Ser		
	900	905	910
10	Lys Pro Tyr Asp Gly Ile Pro Ala Ser Glu Ile Ser Ser Ile Leu Glu		
	915	920	925
	Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr Ile Asp Val Tyr		
	930	935	940
	Met Ile Met Val Lys Cys Trp Met Ile Asp Ala Asp Ser Arg Pro Lys		
15	945	950	955 960
	Phe Arg Glu Leu Ile Ile Glu Phe Ser Lys Met Ala Arg Asp Pro Gln		
	965	970	975
	Arg Tyr Leu Val Ile Gln Gly Asp Glu Arg Met His Leu Pro Ser Pro		
	980	985	990
20	Thr Asp Ser Asn Phe Tyr Arg Ala Leu Met Asp Glu Glu Asp Met Asp		
	995	1000	1005
	Asp Val Val Asp Ala Asp Glu Tyr Leu Ile Pro Gln Gln Gly Phe Phe		
	1010	1015	1020
	Ser Ser Pro Ser Thr Ser Arg Thr Pro Leu Leu Ser Ser Leu Ser Ala		
25	1025	1030	1035 1040
	Thr Ser Asn Asn Ser Thr Val Ala Cys Ile Asp Arg Asn Gly Leu Gln		
	1045	1050	1055
	Ser Cys Pro Ile Lys Glu Asp Ser Phe Leu Gln Arg Tyr Ser Ser Asp		
	1060	1065	1070

Pro Thr Gly Ala Leu Thr Glu Asp Ser Ile Asp Asp Thr Phe Leu Pro  
 1075 1080 1085  
 Val Pro Glu Tyr Ile Asn Gln Ser Val Pro Lys Arg Pro Ala Gly Ser  
 1090 1095 1100  
 5 Val Gln Asn Pro Val Tyr His Asn Gln Pro Leu Asn Pro Ala Pro Ser  
 1105 1110 1115 1120  
 Arg Asp Pro His Tyr Gln Asp Pro His Ser Thr Ala Val Gly Asn Pro  
 1125 1130 1135  
 Glu Tyr Leu Asn Thr Val Gln Pro Thr Cys Val Asn Ser Thr Phe Asp  
 10 1140 1145 1150  
 Ser Pro Ala His Trp Ala Gln Lys Gly Ser His Gln Ile Ser Leu Asp  
 1155 1160 1165  
 Asn Pro Asp Tyr Gln Gln Asp Phe Phe Pro Lys Glu Ala Lys Pro Asn  
 1170 1175 1180  
 15 Gly Ile Phe Lys Gly Ser Thr Ala Glu Asn Ala Glu Tyr Leu Arg Val  
 1185 1190 1195 1200  
 Ala Pro Gln Ser Ser Glu Phe Ile Gly Ala  
 1205 1210

20

<210> 126

<211> 1255

<212> PRT

<213> Homo sapiens

25

<400> 126

Met Glu Leu Ala Ala Leu Cys Arg Trp Gly Leu Leu Leu Ala Leu Leu

1

5

10

15

Pro Pro Gly Ala Ala Ser Thr Gln Val Cys Thr Gly Thr Asp Met Lys

	20	25	30
	Leu Arg Leu Pro Ala Ser Pro Glu Thr His Leu Asp Met Leu Arg His		
	35	40	45
	Leu Tyr Gln Gly Cys Gln Val Val Gln Gly Asn Leu Glu Leu Thr Tyr		
5	50	55	60
	Leu Pro Thr Asn Ala Ser Leu Ser Phe Leu Gln Asp Ile Gln Glu Val		
	65	70	75 80
	Gln Gly Tyr Val Leu Ile Ala His Asn Gln Val Arg Gln Val Pro Leu		
	85	90	95
10	Gln Arg Leu Arg Ile Val Arg Gly Thr Gln Leu Phe Glu Asp Asn Tyr		
	100	105	110
	Ala Leu Ala Val Leu Asp Asn Gly Asp Pro Leu Asn Asn Thr Thr Pro		
	115	120	125
	Val Thr Gly Ala Ser Pro Gly Gly Leu Arg Glu Leu Gln Leu Arg Ser		
15	130	135	140
	Leu Thr Glu Ile Leu Lys Gly Gly Val Leu Ile Gln Arg Asn Pro Gln		
	145	150	155 160
	Leu Cys Tyr Gln Asp Thr Ile Leu Trp Lys Asp Ile Phe His Lys Asn		
	165	170	175
20	Asn Gln Leu Ala Leu Thr Leu Ile Asp Thr Asn Arg Ser Arg Ala Cys		
	180	185	190
	His Pro Cys Ser Pro Met Cys Lys Gly Ser Arg Cys Trp Gly Glu Ser		
	195	200	205
	Ser Glu Asp Cys Gln Ser Leu Thr Arg Thr Val Cys Ala Gly Gly Cys		
25	210	215	220
	Ala Arg Cys Lys Gly Pro Leu Pro Thr Asp Cys Cys His Glu Gln Cys		
	225	230	235 240
	Ala Ala Gly Cys Thr Gly Pro Lys His Ser Asp Cys Leu Ala Cys Leu		
	245	250	255
	425		

His Phe Asn His Ser Gly Ile Cys Glu Leu His Cys Pro Ala Leu Val  
 260 265 270  
 Thr Tyr Asn Thr Asp Thr Phe Glu Ser Met Pro Asn Pro Glu Gly Arg  
 275 280 285  
 5 Tyr Thr Phe Gly Ala Ser Cys Val Thr Ala Cys Pro Tyr Asn Tyr Leu  
 290 295 300  
 Ser Thr Asp Val Gly Ser Cys Thr Leu Val Cys Pro Leu His Asn Gln  
 305 310 315 320  
 Glu Val Thr Ala Glu Asp Gly Thr Gln Arg Cys Glu Lys Cys Ser Lys  
 10 325 330 335  
 Pro Cys Ala Arg Val Cys Tyr Gly Leu Gly Met Glu His Leu Arg Glu  
 340 345 350  
 Val Arg Ala Val Thr Ser Ala Asn Ile Gln Glu Phe Ala Gly Cys Lys  
 355 360 365  
 15 Lys Ile Phe Gly Ser Leu Ala Phe Leu Pro Glu Ser Phe Asp Gly Asp  
 370 375 380  
 Pro Ala Ser Asn Thr Ala Pro Leu Gln Pro Glu Gln Leu Gln Val Phe  
 385 390 395 400  
 Glu Thr Leu Glu Glu Ile Thr Gly Tyr Leu Tyr Ile Ser Ala Trp Pro  
 20 405 410 415  
 Asp Ser Leu Pro Asp Leu Ser Val Phe Gln Asn Leu Gln Val Ile Arg  
 420 425 430  
 Gly Arg Ile Leu His Asn Gly Ala Tyr Ser Leu Thr Leu Gln Gly Leu  
 435 440 445  
 25 Gly Ile Ser Trp Leu Gly Leu Arg Ser Leu Arg Glu Leu Gly Ser Gly  
 450 455 460  
 Leu Ala Leu Ile His His Asn Thr His Leu Cys Phe Val His Thr Val  
 465 470 475 480  
 Pro Trp Asp Gln Leu Phe Arg Asn Pro His Gln Ala Leu Leu His Thr  
 426

485                      490                      495  
 Ala Asn Arg Pro Glu Asp Glu Cys Val Gly Glu Gly Leu Ala Cys His  
                     500                      505                      510  
 Gln Leu Cys Ala Arg Gly His Cys Trp Gly Pro Gly Pro Thr Gln Cys  
 5                      515                      520                      525  
 Val Asn Cys Ser Gln Phe Leu Arg Gly Gln Glu Cys Val Glu Glu Cys  
                     530                      535                      540  
 Arg Val Leu Gln Gly Leu Pro Arg Glu Tyr Val Asn Ala Arg His Cys  
 545                      550                      555                      560  
 10 Leu Pro Cys His Pro Glu Cys Gln Pro Gln Asn Gly Ser Val Thr Cys  
                     565                      570                      575  
 Phe Gly Pro Glu Ala Asp Gln Cys Val Ala Cys Ala His Tyr Lys Asp  
                     580                      585                      590  
 Pro Pro Phe Cys Val Ala Arg Cys Pro Ser Gly Val Lys Pro Asp Leu  
 15                      595                      600                      605  
 Ser Tyr Met Pro Ile Trp Lys Phe Pro Asp Glu Glu Gly Ala Cys Gln  
                     610                      615                      620  
 Pro Cys Pro Ile Asn Cys Thr His Ser Cys Val Asp Leu Asp Asp Lys  
 625                      630                      635                      640  
 20 Gly Cys Pro Ala Glu Gln Arg Ala Ser Pro Leu Thr Ser Ile Val Ser  
                     645                      650                      655  
 Ala Val Val Gly Ile Leu Leu Val Val Val Leu Gly Val Val Phe Gly  
                     660                      665                      670  
 Ile Leu Ile Lys Arg Arg Gln Gln Lys Ile Arg Lys Tyr Thr Met Arg  
 25                      675                      680                      685  
 Arg Leu Leu Gln Glu Thr Glu Leu Val Glu Pro Leu Thr Pro Ser Gly  
                     690                      695                      700  
 Ala Met Pro Asn Gln Ala Gln Met Arg Ile Leu Lys Glu Thr Glu Leu  
 705                      710                      715                      720



Arg Lys Val Lys Val Leu Gly Ser Gly Ala Phe Gly Thr Val Tyr Lys  
 725 730 735  
 Gly Ile Trp Ile Pro Asp Gly Glu Asn Val Lys Ile Pro Val Ala Ile  
 740 745 750  
 5 Lys Val Leu Arg Glu Asn Thr Ser Pro Lys Ala Asn Lys Glu Ile Leu  
 755 760 765  
 Asp Glu Ala Tyr Val Met Ala Gly Val Gly Ser Pro Tyr Val Ser Arg  
 770 775 780  
 Leu Leu Gly Ile Cys Leu Thr Ser Thr Val Gln Leu Val Thr Gln Leu  
 10 785 790 795 800  
 Met Pro Tyr Gly Cys Leu Leu Asp His Val Arg Glu Asn Arg Gly Arg  
 805 810 815  
 Leu Gly Ser Gln Asp Leu Leu Asn Trp Cys Met Gln Ile Ala Lys Gly  
 820 825 830  
 15 Met Ser Tyr Leu Glu Asp Val Arg Leu Val His Arg Asp Leu Ala Ala  
 835 840 845  
 Arg Asn Val Leu Val Lys Ser Pro Asn His Val Lys Ile Thr Asp Phe  
 850 855 860  
 Gly Leu Ala Arg Leu Leu Asp Ile Asp Glu Thr Glu Tyr His Ala Asp  
 20 865 870 875 880  
 Gly Gly Lys Val Pro Ile Lys Trp Met Ala Leu Glu Ser Ile Leu Arg  
 885 890 895  
 Arg Arg Phe Thr His Gln Ser Asp Val Trp Ser Tyr Gly Val Thr Val  
 900 905 910  
 25 Trp Glu Leu Met Thr Phe Gly Ala Lys Pro Tyr Asp Gly Ile Pro Ala  
 915 920 925  
 Arg Glu Ile Pro Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro  
 930 935 940  
 Pro Ile Cys Thr Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met  
 428

	945	950	955	960
	Ile Asp Ser Glu Cys Arg Pro Arg Phe Arg Glu Leu Val Ser Glu Phe			
	965	970	975	
	Ser Arg Met Ala Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu			
5	980	985	990	
	Asp Leu Gly Pro Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu			
	995	1000	1005	
	Leu Glu Asp Asp Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu			
	1010	1015	1020	
10	Val Pro Gln Gln Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly			
	1025	1030	1035	1040
	Gly Met Val His His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly			
	1045	1050	1055	
	Gly Asp Leu Thr Leu Gly Leu Glu Pro Ser Glu Glu Glu Ala Pro Arg			
15	1060	1065	1070	
	Ser Pro Leu Ala Pro Ser Glu Gly Ala Gly Ser Asp Val Phe Asp Gly			
	1075	1080	1085	
	Asp Leu Gly Met Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His			
	1090	1095	1100	
20	Asp Pro Ser Pro Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu			
	1105	1110	1115	1120
	Pro Ser Glu Thr Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln			
	1125	1130	1135	
	Pro Glu Tyr Val Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro			
25	1140	1145	1150	
	Arg Glu Gly Pro Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu			
	1155	1160	1165	
	Arg Ala Lys Thr Leu Ser Pro Gly Lys Asn Gly Val Val Lys Asp Val			
	1170	1175	1180	



	85	90	95
	Gly Leu Asn Ala Met Glu Cys Ala Leu His Leu Glu Lys Asn Val Asn		
	100	105	110
	Gln Ser Leu Leu Glu Leu His Lys Leu Ala Thr Asp Lys Asn Asp Pro		
5	115	120	125
	His Leu Cys Asp Phe Ile Glu Thr His Tyr Leu Asn Glu Gln Val Lys		
	130	135	140
	Ala Ile Lys Glu Leu Gly Asp His Val Thr Asn Leu Arg Lys Met Gly		
	145	150	155 160
10	Ala Pro Glu Ser Gly Leu Ala Glu Tyr Leu Phe Asp Lys His Thr Trp		
	165	170	175
	Glu Thr Val Ile Met Lys Ala Lys Pro Arg Ala Asn Phe Pro		
	180	185	190

15

<210> 128  
 <211> 175  
 <212> PRT  
 <213> Homo sapiens

20

<400> 128

Met Ser Ser Gln Ile Arg Gln Asn Tyr Ser Thr Asp Val Glu Ala Ala			
1	5	10	15
Val Asn Ser Leu Val Asn Leu Tyr Leu Gln Ala Ser Tyr Thr Tyr Leu			
25	20	25	30
Ser Leu Gly Phe Tyr Phe Asp Arg Asp Asp Val Ala Leu Glu Gly Val			
35	40	45	
Ser His Phe Phe Arg Glu Leu Ala Glu Glu Lys Arg Glu Gly Tyr Glu			
50	55	60	

Arg Leu Leu Lys Met Gln Asn Gln Arg Gly Gly Arg Ala Leu Phe Gln  
 65                      70                      75                      80  
 Asp Ile Lys Lys Pro Ala Glu Asp Glu Trp Gly Lys Thr Pro Asp Ala  
                     85                      90                      95  
 5 Met Lys Ala Ala Met Ala Leu Glu Lys Lys Leu Asn Gln Ala Leu Leu  
                     100                      105                      110  
 Asp Leu His Ala Leu Gly Ser Ala Arg Thr Asp Pro His Leu Cys Asp  
                     115                      120                      125  
 Phe Leu Glu Thr His Phe Leu Asp Glu Glu Val Lys Leu Ile Lys Lys  
 10                      130                      135                      140  
 Met Gly Asp His Leu Thr Asn Leu His Arg Leu Gly Gly Pro Glu Ala  
 145                      150                      155                      160  
 Gly Leu Gly Glu Tyr Leu Phe Glu Arg Leu Thr Leu Lys His Asp  
                     165                      170                      175

15

<210> 129

<211> 535

<212> PRT

20 <213> Homo sapiens

<400> 129

Met Leu Gly Pro Cys Met Leu Leu Leu Leu Leu Leu Gly Leu Arg  
 1                      5                      10                      15  
 25 Leu Gln Leu Ser Leu Gly Ile Ile Leu Val Glu Glu Glu Asn Pro Asp  
                     20                      25                      30  
 Phe Trp Asn Arg Glu Ala Ala Glu Ala Leu Gly Ala Ala Lys Lys Leu  
                     35                      40                      45  
 Gln Pro Ala Gln Thr Ala Ala Lys Asn Leu Ile Ile Phe Leu Gly Asp  
 432

	50	55	60	
	Gly Met Gly Val Ser Thr Val Thr Ala Ala Arg Ile Leu Lys Gly Gln			
	65	70	75	80
	Lys Lys Asp Lys Leu Gly Pro Glu Ile Pro Leu Ala Met Asp Arg Phe			
5	85	90	95	
	Pro Tyr Val Ala Leu Ser Lys Thr Tyr Asn Val Asp Lys His Val Pro			
	100	105	110	
	Asp Ser Gly Ala Thr Ala Thr Ala Tyr Leu Cys Gly Val Lys Gly Asn			
	115	120	125	
10	Phe Gln Thr Ile Gly Leu Ser Ala Ala Ala Arg Phe Asn Gln Cys Asn			
	130	135	140	
	Thr Thr Arg Gly Asn Glu Val Ile Ser Val Met Asn Arg Ala Lys Lys			
	145	150	155	160
	Ala Gly Lys Ser Val Gly Val Val Thr Thr Thr Arg Val Gln His Ala			
15	165	170	175	
	Ser Pro Ala Gly Thr Tyr Ala His Thr Val Asn Arg Asn Trp Tyr Ser			
	180	185	190	
	Asp Ala Asp Val Pro Ala Ser Ala Arg Gln Glu Gly Cys Gln Asp Ile			
	195	200	205	
20	Ala Thr Gln Leu Ile Ser Asn Met Asp Ile Asp Val Ile Leu Gly Gly			
	210	215	220	
	Gly Arg Lys Tyr Met Phe Arg Met Gly Thr Pro Asp Pro Glu Tyr Pro			
	225	230	235	240
	Asp Asp Tyr Ser Gln Gly Gly Thr Arg Leu Asp Gly Lys Asn Leu Val			
25	245	250	255	
	Gln Glu Trp Leu Ala Lys Arg Gln Gly Ala Arg Tyr Val Trp Asn Arg			
	260	265	270	
	Thr Glu Leu Met Gln Ala Ser Leu Asp Pro Ser Val Ala His Leu Met			
	275	280	285	

Gly Leu Phe Glu Pro Gly Asp Met Lys Tyr Glu Ile His Arg Asp Ser  
 290 295 300  
 Thr Leu Asp Pro Ser Leu Met Glu Met Thr Glu Ala Ala Leu Arg Leu  
 305 310 315 320  
 5 Leu Ser Arg Asn Pro Arg Gly Phe Phe Leu Phe Val Glu Gly Gly Arg  
 325 330 335  
 Ile Asp His Gly His His Glu Ser Arg Ala Tyr Arg Ala Leu Thr Glu  
 340 345 350  
 Thr Ile Met Phe Asp Asp Ala Ile Glu Arg Ala Gly Gln Leu Thr Ser  
 10 355 360 365  
 Glu Glu Asp Thr Leu Ser Leu Val Thr Ala Asp His Ser His Val Phe  
 370 375 380  
 Ser Phe Gly Gly Tyr Pro Leu Arg Gly Ser Ser Ile Phe Gly Leu Ala  
 385 390 395 400  
 15 Pro Gly Lys Ala Arg Asp Arg Lys Ala Tyr Thr Val Leu Leu Tyr Gly  
 405 410 415  
 Asn Gly Pro Gly Tyr Val Leu Lys Asp Gly Ala Arg Pro Asp Val Thr  
 420 425 430  
 Glu Ser Glu Ser Gly Ser Pro Glu Tyr Arg Gln Gln Ser Ala Val Pro  
 20 435 440 445  
 Leu Asp Glu Glu Thr His Ala Gly Glu Asp Val Ala Val Phe Ala Arg  
 450 455 460  
 Gly Pro Gln Ala His Leu Val His Gly Val Gln Glu Gln Thr Phe Ile  
 465 470 475 480  
 25 Ala His Val Met Ala Phe Ala Ala Cys Leu Glu Pro Tyr Thr Ala Cys  
 485 490 495  
 Asp Leu Ala Pro Pro Ala Gly Thr Thr Asp Ala Ala His Pro Gly Arg  
 500 505 510  
 Ser Val Val Pro Ala Leu Leu Pro Leu Leu Ala Gly Thr Leu Leu Leu  
 434

	515	520	525
	Leu Glu Thr Ala Thr Ala Pro		
	530	535	
5			
	<210> 130		
	<211> 461		
	<212> PRT		
	<213> Homo sapiens		
10			
	<400> 130		
	Met Asn Asn Phe Gly Asn Glu Glu Phe Asp Cys His Phe Leu Asp Glu		
	1	5	10 15
	Gly Phe Thr Ala Lys Asp Ile Leu Asp Gln Lys Ile Asn Glu Val Ser		
15	20	25	30
	Ser Ser Asp Asp Lys Asp Ala Phe Tyr Val Ala Asp Leu Gly Asp Ile		
	35	40	45
	Leu Lys Lys His Leu Arg Trp Leu Lys Ala Leu Pro Arg Val Thr Pro		
	50	55	60
20	Phe Tyr Ala Val Lys Cys Asn Asp Ser Lys Ala Ile Val Lys Thr Leu		
	65	70	75 80
	Ala Ala Thr Gly Thr Gly Phe Asp Cys Ala Ser Lys Thr Glu Ile Gln		
	85	90	95
	Leu Val Gln Ser Leu Gly Val Pro Pro Glu Arg Ile Ile Tyr Ala Asn		
25	100	105	110
	Pro Cys Lys Gln Val Ser Gln Ile Lys Tyr Ala Ala Asn Asn Gly Val		
	115	120	125
	Gln Met Met Thr Phe Asp Ser Glu Val Glu Leu Met Lys Val Ala Arg		
	130	135	140
	435		



Ala His Pro Lys Ala Lys Leu Val Leu Arg Ile Ala Thr Asp Asp Ser  
 145                      150                      155                      160  
 Lys Ala Val Cys Arg Leu Ser Val Lys Phe Gly Ala Thr Leu Arg Thr  
                     165                      170                      175  
 5 Ser Arg Leu Leu Leu Glu Arg Ala Lys Glu Leu Asn Ile Asp Val Val  
                     180                      185                      190  
 Gly Val Ser Phe His Val Gly Ser Gly Cys Thr Asp Pro Glu Thr Phe  
                     195                      200                      205  
 Val Gln Ala Ile Ser Asp Ala Arg Cys Val Phe Asp Met Gly Ala Glu  
 10                      210                      215                      220  
 Val Gly Phe Ser Met Tyr Leu Leu Asp Ile Gly Gly Gly Phe Pro Gly  
 225                      230                      235                      240  
 Ser Glu Asp Val Lys Leu Lys Phe Glu Glu Ile Thr Gly Val Ile Asn  
                     245                      250                      255  
 15 Pro Ala Leu Asp Lys Tyr Phe Pro Ser Asp Ser Gly Val Arg Ile Ile  
                     260                      265                      270  
 Ala Glu Pro Gly Arg Tyr Tyr Val Ala Ser Ala Phe Thr Leu Ala Val  
                     275                      280                      285  
 Asn Ile Ile Ala Lys Lys Ile Val Leu Lys Glu Gln Thr Gly Ser Asp  
 20                      290                      295                      300  
 Asp Glu Asp Glu Ser Ser Glu Gln Thr Phe Met Tyr Tyr Val Asn Asp  
 305                      310                      315                      320  
 Gly Val Tyr Gly Ser Phe Asn Cys Ile Leu Tyr Asp His Ala His Val  
                     325                      330                      335  
 25 Lys Pro Leu Leu Gln Lys Arg Pro Lys Pro Asp Glu Lys Tyr Tyr Ser  
                     340                      345                      350  
 Ser Ser Ile Trp Gly Pro Thr Cys Asp Gly Leu Asp Arg Ile Val Glu  
                     355                      360                      365  
 Arg Cys Asp Leu Pro Glu Met His Val Gly Asp Trp Met Leu Phe Glu  
 436

370                      375                      380  
 Asn Met Gly Ala Tyr Thr Val Ala Ala Ala Ser Thr Phe Asn Gly Phe  
 385                      390                      395                      400  
 Gln Arg Pro Thr Ile Tyr Tyr Val Met Ser Gly Pro Ala Trp Gln Leu  
 5                      405                      410                      415  
 Met Gln Gln Phe Gln Asn Pro Asp Phe Pro Pro Glu Val Glu Glu Gln  
                     420                      425                      430  
 Asp Ala Ser Thr Leu Pro Val Ser Cys Ala Trp Glu Ser Gly Met Lys  
                     435                      440                      445  
 10 Arg His Arg Ala Ala Cys Ala Ser Ala Ser Ile Asn Val  
                     450                      455                      460

<210> 131  
 15 <211> 1148

<212> PRT

<213> Homo sapiens

<400> 131  
 20 Met Pro Leu Phe Lys Asn Thr Ser Val Ser Ser Leu Tyr Ser Gly Cys  
     1                      5                      10                      15  
 Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Arg Val  
                     20                      25                      30  
 Asp Ala Val Cys Thr His Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp  
 25                      35                      40                      45  
 Arg Glu Arg Leu Tyr Trp Lys Leu Ser Gln Leu Thr His Gly Ile Thr  
                     50                      55                      60  
 Glu Leu Gly Pro Tyr Thr Leu Asp Arg His Ser Leu Tyr Val Asn Gly  
 65                      70                      75                      80

Phe Thr His Gln Ser Ser Met Thr Thr Thr Arg Thr Pro Asp Thr Ser  
                     85                    90                    95  
 Thr Met His Leu Ala Thr Ser Arg Thr Pro Ala Ser Leu Ser Gly Pro  
                     100                    105                    110  
 5 Thr Thr Ala Ser Pro Leu Leu Val Leu Phe Thr Ile Asn Phe Thr Ile  
                     115                    120                    125  
 Thr Asn Leu Arg Tyr Glu Glu Asn Met His His Pro Gly Ser Arg Lys  
                     130                    135                    140  
 Phe Asn Thr Thr Glu Arg Val Leu Gln Gly Leu Leu Arg Pro Val Phe  
 10 145                    150                    155                    160  
 Lys Asn Thr Ser Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu  
                     165                    170                    175  
 Leu Arg Pro Lys Lys Asp Gly Ala Ala Thr Lys Val Asp Ala Ile Cys  
                     180                    185                    190  
 15 Thr Tyr Arg Pro Asp Pro Lys Ser Pro Gly Leu Asp Arg Glu Gln Leu  
                     195                    200                    205  
 Tyr Trp Glu Leu Ser Gln Leu Thr His Ser Ile Thr Glu Leu Gly Pro  
                     210                    215                    220  
 Tyr Thr Leu Asp Arg Asp Ser Leu Tyr Val Asn Gly Phe Thr Gln Arg  
 20 225                    230                    235                    240  
 Ser Ser Val Pro Thr Thr Ser Ile Pro Gly Thr Pro Thr Val Asp Leu  
                     245                    250                    255  
 Gly Thr Ser Gly Thr Pro Val Ser Lys Pro Gly Pro Ser Ala Ala Ser  
                     260                    265                    270  
 25 Pro Leu Leu Val Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg  
                     275                    280                    285  
 Tyr Glu Glu Asn Met Gln His Pro Gly Ser Arg Lys Phe Asn Thr Thr  
                     290                    295                    300  
 Glu Arg Val Leu Gln Gly Leu Leu Arg Ser Leu Phe Lys Ser Thr Ser  
                     438

	305	310	315	320
	Val Gly Pro Leu Tyr Ser Gly Cys Arg Leu Thr Leu Leu Arg Pro Glu			
	325	330	335	
	Lys Asp Gly Thr Ala Thr Gly Val Asp Ala Ile Cys Thr His His Pro			
5	340	345	350	
	Asp Pro Lys Ser Pro Arg Leu Asp Arg Glu Gln Leu Tyr Trp Glu Leu			
	355	360	365	
	Ser Gln Leu Thr His Asn Ile Thr Glu Leu Gly His Tyr Ala Leu Asp			
	370	375	380	
10	Asn Asp Ser Leu Phe Val Asn Gly Phe Thr His Arg Ser Ser Val Ser			
	385	390	395	400
	Thr Thr Ser Thr Pro Gly Thr Pro Thr Val Tyr Leu Gly Ala Ser Lys			
	405	410	415	
	Thr Pro Ala Ser Ile Phe Gly Pro Ser Ala Ala Ser His Leu Leu Ile			
15	420	425	430	
	Leu Phe Thr Leu Asn Phe Thr Ile Thr Asn Leu Arg Tyr Glu Glu Asn			
	435	440	445	
	Met Trp Pro Gly Ser Arg Lys Phe Asn Thr Thr Glu Arg Val Leu Gln			
	450	455	460	
20	Gly Leu Leu Arg Pro Leu Phe Lys Asn Thr Ser Val Gly Pro Leu Tyr			
	465	470	475	480
	Ser Gly Ser Arg Leu Thr Leu Leu Arg Pro Glu Lys Asp Gly Glu Ala			
	485	490	495	
	Thr Gly Val Asp Ala Ile Cys Thr His Arg Pro Asp Pro Thr Gly Pro			
25	500	505	510	
	Gly Leu Asp Arg Glu Gln Leu Tyr Leu Glu Leu Ser Gln Leu Thr His			
	515	520	525	
	Ser Ile Thr Glu Leu Gly Pro Tyr Thr Leu Asp Arg Asp Ser Leu Tyr			
	530	535	540	
		439		

Val Asn Gly Phe Thr His Arg Ser Ser Val Pro Thr Thr Ser Thr Gly  
 545                      550                      555                      560  
 Val Val Ser Glu Glu Pro Phe Thr Leu Asn Phe Thr Ile Asn Asn Leu  
                     565                      570                      575  
 5 Arg Tyr Met Ala Asp Met Gly Gln Pro Gly Ser Leu Lys Phe Asn Ile  
                     580                      585                      590  
 Thr Asp Asn Val Met Lys His Leu Leu Ser Pro Leu Phe Gln Arg Ser  
                     595                      600                      605  
 Ser Leu Gly Ala Arg Tyr Thr Gly Cys Arg Val Ile Ala Leu Arg Ser  
 10            610                      615                      620  
 Val Lys Asn Gly Ala Glu Thr Arg Val Asp Leu Leu Cys Thr Tyr Leu  
 625                      630                      635                      640  
 Gln Pro Leu Ser Gly Pro Gly Leu Pro Ile Lys Gln Val Phe His Glu  
                     645                      650                      655  
 15 Leu Ser Gln Gln Thr His Gly Ile Thr Arg Leu Gly Pro Tyr Ser Leu  
                     660                      665                      670  
 Asp Lys Asp Ser Leu Tyr Leu Asn Gly Tyr Asn Glu Pro Gly Leu Asp  
                     675                      680                      685  
 Glu Pro Pro Thr Thr Pro Lys Pro Ala Thr Thr Phe Leu Pro Pro Leu  
 20            690                      695                      700  
 Ser Glu Ala Thr Thr Ala Met Gly Tyr His Leu Lys Thr Leu Thr Leu  
 705                      710                      715                      720  
 Asn Phe Thr Ile Ser Asn Leu Gln Tyr Ser Pro Asp Met Gly Lys Gly  
                     725                      730                      735  
 25 Ser Ala Thr Phe Asn Ser Thr Glu Gly Val Leu Gln His Leu Leu Arg  
                     740                      745                      750  
 Pro Leu Phe Gln Lys Ser Ser Met Gly Pro Phe Tyr Leu Gly Cys Gln  
                     755                      760                      765  
 Leu Ile Ser Leu Arg Pro Glu Lys Asp Gly Ala Ala Thr Gly Val Asp  
 440

	770	775	780
	Thr Thr Cys Thr Tyr His Pro Asp Pro Val Gly Pro Gly Leu Asp Ile		
	785	790	795 800
	Gln Gln Leu Tyr Trp Glu Leu Ser Gln Leu Thr His Gly Val Thr Gln		
5	805	810	815
	Leu Gly Phe Tyr Val Leu Asp Arg Asp Ser Leu Phe Ile Asn Gly Tyr		
	820	825	830
	Ala Pro Gln Asn Leu Ser Ile Arg Gly Glu Tyr Gln Ile Asn Phe His		
	835	840	845
10	Ile Val Asn Trp Asn Leu Ser Asn Pro Asp Pro Thr Ser Ser Glu Tyr		
	850	855	860
	Ile Thr Leu Leu Arg Asp Ile Gln Asp Lys Val Thr Thr Leu Tyr Lys		
	865	870	875 880
	Gly Ser Gln Leu His Asp Thr Phe Arg Phe Cys Leu Val Thr Asn Leu		
15	885	890	895
	Thr Met Asp Ser Val Leu Val Thr Val Lys Ala Leu Phe Ser Ser Asn		
	900	905	910
	Leu Asp Pro Ser Leu Val Glu Gln Val Phe Leu Asp Lys Thr Leu Asn		
	915	920	925
20	Ala Ser Phe His Trp Leu Gly Ser Thr Tyr Gln Leu Val Asp Ile His		
	930	935	940
	Val Thr Glu Met Glu Ser Ser Val Tyr Gln Pro Thr Ser Ser Ser Ser		
	945	950	955 960
	Thr Gln His Phe Tyr Pro Asn Phe Thr Ile Thr Asn Leu Pro Tyr Ser		
25	965	970	975
	Gln Asp Lys Ala Gln Pro Gly Thr Thr Asn Tyr Gln Arg Asn Lys Arg		
	980	985	990
	Asn Ile Glu Asp Ala Leu Asn Gln Leu Phe Arg Asn Ser Ser Ile Lys		
	995	1000	1005

Ser Tyr Phe Ser Asp Cys Gln Val Ser Thr Phe Arg Ser Val Pro Asn  
 1010 1015 1020  
 Arg His His Thr Gly Val Asp Ser Leu Cys Asn Phe Ser Pro Leu Ala  
 1025 1030 1035 1040  
 5 Arg Arg Val Asp Arg Val Ala Ile Tyr Glu Glu Phe Leu Arg Met Thr  
 1045 1050 1055  
 Arg Asn Gly Thr Gln Leu Gln Asn Phe Thr Leu Asp Arg Ser Ser Val  
 1060 1065 1070  
 Leu Val Asp Gly Tyr Ser Pro Asn Arg Asn Glu Pro Leu Thr Gly Asn  
 10 1075 1080 1085  
 Ser Asp Leu Pro Phe Trp Ala Val Ile Phe Ile Gly Leu Ala Gly Leu  
 1090 1095 1100  
 Leu Gly Leu Ile Thr Cys Leu Ile Cys Gly Val Leu Val Thr Thr Arg  
 1105 1110 1115 1120  
 15 Arg Arg Lys Lys Glu Gly Glu Tyr Asn Val Gln Gln Gln Cys Pro Gly  
 1125 1130 1135  
 Tyr Tyr Gln Ser His Leu Asp Leu Glu Asp Leu Gln  
 1140 1145

20

<210> 132  
 <211> 526  
 <212> PRT  
 <213> Homo sapiens

25

<400> 132  
 Met Gly His Leu Ser Ala Pro Leu His Arg Val Arg Val Pro Trp Gln  
 1 5 10 15  
 Gly Leu Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr

	20	25	30
	Thr Ala Gln Leu Thr Thr Glu Ser Met Pro Phe Asn Val Ala Glu Gly		
	35	40	45
	Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln Gln Leu Phe Gly		
5	50	55	60
	Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Arg Gln Ile Val		
	65	70	75 80
	Gly Tyr Ala Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Asn Ser		
	85	90	95
10	Gly Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val		
	100	105	110
	Thr Gln Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp		
	115	120	125
	Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu		
15	130	135	140
	Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys		
	145	150	155 160
	Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asp Thr Thr Tyr		
	165	170	175
20	Leu Trp Trp Ile Asn Asn Gln Ser Leu Pro Val Ser Pro Arg Leu Gln		
	180	185	190
	Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Leu Ser Val Thr Arg Asn		
	195	200	205
	Asp Thr Gly Pro Tyr Glu Cys Glu Ile Gln Asn Pro Val Ser Ala Asn		
25	210	215	220
	Arg Ser Asp Pro Val Thr Leu Asn Val Thr Tyr Gly Pro Asp Thr Pro		
	225	230	235 240
	Thr Ile Ser Pro Ser Asp Thr Tyr Tyr Arg Pro Gly Ala Asn Leu Ser		
	245	250	255



Leu Ser Cys Tyr Ala Ala Ser Asn Pro Pro Ala Gln Tyr Ser Trp Leu  
 260 265 270  
 Ile Asn Gly Thr Phe Gln Gln Ser Thr Gln Glu Leu Phe Ile Pro Asn  
 275 280 285  
 5 Ile Thr Val Asn Asn Ser Gly Ser Tyr Thr Cys His Ala Asn Asn Ser  
 290 295 300  
 Val Thr Gly Cys Asn Arg Thr Thr Val Lys Thr Ile Ile Val Thr Glu  
 305 310 315 320  
 Leu Ser Pro Val Val Ala Lys Pro Gln Ile Lys Ala Ser Lys Thr Thr  
 10 325 330 335  
 Val Thr Gly Asp Lys Asp Ser Val Asn Leu Thr Cys Ser Thr Asn Asp  
 340 345 350  
 Thr Gly Ile Ser Ile Arg Trp Phe Phe Lys Asn Gln Ser Leu Pro Ser  
 355 360 365  
 15 Ser Glu Arg Met Lys Leu Ser Gln Gly Asn Thr Thr Leu Ser Ile Asn  
 370 375 380  
 Pro Val Lys Arg Glu Asp Ala Gly Thr Tyr Trp Cys Glu Val Phe Asn  
 385 390 395 400  
 Pro Ile Ser Lys Asn Gln Ser Asp Pro Ile Met Leu Asn Val Asn Tyr  
 20 405 410 415  
 Asn Ala Leu Pro Gln Glu Asn Gly Leu Ser Pro Gly Ala Ile Ala Gly  
 420 425 430  
 Ile Val Ile Gly Val Val Ala Leu Val Ala Leu Ile Ala Val Ala Leu  
 435 440 445  
 25 Ala Cys Phe Leu His Phe Gly Lys Thr Gly Arg Ala Ser Asp Gln Arg  
 450 455 460  
 Asp Leu Thr Glu His Lys Pro Ser Val Ser Asn His Thr Gln Asp His  
 465 470 475 480  
 Ser Asn Asp Pro Pro Asn Lys Met Asn Glu Val Thr Tyr Ser Thr Leu

	485	490	495
	Asn Phe Glu Ala Gln Gln Pro Thr Gln Pro Thr Ser Ala Ser Pro Ser		
	500	505	510
	Leu Thr Ala Thr Glu Ile Ile Tyr Ser Glu Val Lys Lys Gln		
5	515	520	525
	<210> 133		
	<211> 212		
10	<212> PRT		
	<213> Homo sapiens		
	<400> 133		
	Met Gly Pro Pro Ser Ala Pro Pro His Arg Glu Cys Ile Pro Trp Gln		
15	1	5	10 15
	Gly Leu Leu Leu Thr Ala Ser Leu Leu Asn Phe Trp Asn Pro Pro Thr		
	20	25	30
	Thr Ala Lys Leu Thr Ile Glu Ser Met Pro Leu Ser Val Ala Glu Gly		
	35	40	45
20	Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln His Leu Phe Gly		
	50	55	60
	Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val		
	65	70	75 80
	Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Ala Ala Tyr Ser		
25	85	90	95
	Gly Arg Glu Thr Ile Tyr Thr Asn Ala Ser Leu Leu Ile Gln Asn Val		
	100	105	110
	Thr Gln Asn Asp Ile Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp		
	115	120	125
	445		

Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Gln Glu Asn  
 130 135 140  
 Ala Pro Gly Leu Pro Val Gly Ala Val Ala Gly Ile Val Thr Gly Val  
 145 150 155 160  
 5 Leu Val Gly Val Ala Leu Val Ala Ala Leu Val Cys Phe Leu Leu Leu  
 165 170 175  
 Ala Lys Thr Gly Arg Pro Trp Ser Leu Pro Gln Leu Cys Leu Leu Asp  
 180 185 190  
 Val Pro Ser Leu His Cys Leu Gly Pro Pro Thr Gln Pro Gln Asp Ser  
 10 195 200 205  
 Ser Phe His Leu  
 210

15 <210> 134  
 <211> 244  
 <212> PRT  
 <213> Homo sapiens

20 <400> 134  
 Met Gly Pro Pro Ser Ala Ala Pro Arg Gly Gly His Arg Pro Trp Gln  
 1 5 10 15  
 Gly Leu Leu Ile Thr Ala Ser Leu Leu Thr Phe Trp Asp Pro Pro Thr  
 20 25 30  
 25 Thr Val Gln Phe Thr Ile Glu Ala Leu Pro Ser Ser Ala Ala Glu Gly  
 35 40 45  
 Lys Asp Val Leu Leu Leu Ala Cys Asn Ile Ser Glu Thr Ile Gln Ala  
 50 55 60  
 Tyr Tyr Trp His Lys Gly Lys Thr Ala Glu Gly Ser Pro Leu Ile Ala  
 446

	65		70		75		80
	Gly Tyr Ile Thr Asp Ile Gln Ala Asn Ile Pro Gly Ala Ala Tyr Ser						
		85		90		95	
	Gly Arg Glu Gln Val Tyr Pro Asn Gly Ser Leu Leu Phe Gln Asn Ile						
5		100		105		110	
	Thr Leu Glu Asp Ala Gly Ser Tyr Thr Leu Arg Thr Ile Asn Ala Ser						
		115		120		125	
	Tyr Asp Ser Asp Gln Ala Thr Gly Gln Leu His Val His Gln Asn Asn						
		130		135		140	
10	Val Pro Gly Leu Pro Val Gly Ala Val Ala Gly Ile Val Thr Gly Val						
		145		150		155	160
	Leu Val Gly Val Ala Leu Val Ala Ala Leu Val Cys Phe Leu Leu Leu						
		165		170		175	
	Ser Arg Thr Gly Arg Ala Ser Ile Gln Arg Asp Leu Arg Glu Gln Pro						
15		180		185		190	
	Pro Pro Ala Ser Thr Pro Gly His Gly Pro Ser His Arg Ser Thr Phe						
		195		200		205	
	Ser Ala Pro Leu Pro Ser Pro Arg Thr Ala Thr Pro Ile Tyr Val Glu						
		210		215		220	
20	Phe Leu Tyr Ser Asp Ala Asn Ile Tyr Cys Gln Ile Asp His Lys Ala						
		225		230		235	240
	Asp Val Val Ser						

25

<210> 135

<211> 344

<212> PRT

<213> Homo sapiens

<400> 135

Met Gly Pro Pro Ser Ala Pro Pro Cys Arg Leu His Val Pro Trp Lys  
1 5 10 15  
5 Glu Val Leu Leu Thr Ala Ser Leu Leu Thr Phe Trp Asn Pro Pro Thr  
20 25 30  
Thr Ala Lys Leu Thr Ile Glu Ser Thr Pro Phe Asn Val Ala Glu Gly  
35 40 45  
Lys Glu Val Leu Leu Leu Ala His Asn Leu Pro Gln Asn Arg Ile Gly  
10 50 55 60  
Tyr Ser Trp Tyr Lys Gly Glu Arg Val Asp Gly Asn Ser Leu Ile Val  
65 70 75 80  
Gly Tyr Val Ile Gly Thr Gln Gln Ala Thr Pro Gly Pro Ala Tyr Ser  
85 90 95  
15 Gly Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Ile Gln Asn Val  
100 105 110  
Thr Gln Asn Asp Thr Gly Phe Tyr Thr Leu Gln Val Ile Lys Ser Asp  
115 120 125  
Leu Val Asn Glu Glu Ala Thr Gly Gln Phe His Val Tyr Pro Glu Leu  
20 130 135 140  
Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys  
145 150 155 160  
Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Val Gln Asn Thr Thr Tyr  
165 170 175  
25 Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Arg Leu Gln  
180 185 190  
Leu Ser Asn Gly Asn Met Thr Leu Thr Leu Leu Ser Val Lys Arg Asn  
195 200 205  
Asp Ala Gly Ser Tyr Glu Cys Glu Ile Gln Asn Pro Ala Ser Ala Asn



Ser Ala Gln Thr Asn Ile Asp Val Val Pro Phe Asn Val Ala Glu Gly  
 35 40 45  
 Lys Glu Val Leu Leu Val Val His Asn Glu Ser Gln Asn Leu Tyr Gly  
 50 55 60  
 5 Tyr Asn Trp Tyr Lys Gly Glu Arg Val His Ala Asn Tyr Arg Ile Ile  
 65 70 75 80  
 Gly Tyr Val Lys Asn Ile Ser Gln Glu Asn Ala Pro Gly Pro Ala His  
 85 90 95  
 Asn Gly Arg Glu Thr Ile Tyr Pro Asn Gly Thr Leu Leu Ile Gln Asn  
 10 100 105 110  
 Val Thr His Asn Asp Ala Gly Phe Tyr Thr Leu His Val Ile Lys Glu  
 115 120 125  
 Asn Leu Val Asn Glu Glu Val Thr Arg Gln Phe Tyr Val Phe Ser Glu  
 130 135 140  
 15 Pro Pro Lys Pro Ser Ile Thr Ser Asn Asn Phe Asn Pro Val Glu Asn  
 145 150 155 160  
 Lys Asp Ile Val Val Leu Thr Cys Gln Pro Glu Thr Gln Asn Thr Thr  
 165 170 175  
 Tyr Leu Trp Trp Val Asn Asn Gln Ser Leu Leu Val Ser Pro Arg Leu  
 20 180 185 190  
 Leu Leu Ser Thr Asp Asn Arg Thr Leu Val Leu Leu Ser Ala Thr Lys  
 195 200 205  
 Asn Asp Ile Gly Pro Tyr Glu Cys Glu Ile Gln Asn Pro Val Gly Ala  
 210 215 220  
 25 Ser Arg Ser Asp Pro Val Thr Leu Asn Val Arg Tyr Glu Ser Val Gln  
 225 230 235 240  
 Ala Ser Ser Pro Asp Leu Ser Ala Gly Thr Ala Val Ser Ile Met Ile  
 245 250 255  
 Gly Val Leu Ala Gly Met Ala Leu Ile  
 450

<210> 137

5 <211> 349

<212> PRT

<213> Homo sapiens

<400> 137

10 Met Gly Pro Ile Ser Ala Pro Ser Cys Arg Trp Arg Ile Pro Trp Gln  
 1 5 10 15  
 Gly Leu Leu Leu Thr Ala Ser Leu Phe Thr Phe Trp Asn Pro Pro Thr  
 20 25 30  
 Thr Ala Gln Leu Thr Ile Glu Ala Val Pro Ser Asn Ala Ala Glu Gly  
 15 35 40 45  
 Lys Glu Val Leu Leu Leu Val His Asn Leu Pro Gln Asp Pro Arg Gly  
 50 55 60  
 Tyr Asn Trp Tyr Lys Gly Glu Thr Val Asp Ala Asn Arg Arg Ile Ile  
 65 70 75 80  
 20 Gly Tyr Val Ile Ser Asn Gln Gln Ile Thr Pro Gly Pro Ala Tyr Ser  
 85 90 95  
 Asn Arg Glu Thr Ile Tyr Pro Asn Ala Ser Leu Leu Met Arg Asn Val  
 100 105 110  
 Thr Arg Asn Asp Thr Gly Ser Tyr Thr Leu Gln Val Ile Lys Leu Asn  
 25 115 120 125  
 Leu Met Ser Glu Glu Val Thr Gly Gln Phe Ser Val His Pro Glu Thr  
 130 135 140  
 Pro Lys Pro Ser Ile Ser Ser Asn Asn Ser Asn Pro Val Glu Asp Lys  
 145 150 155 160  
 451



Asp Ala Val Ala Phe Thr Cys Glu Pro Glu Thr Gln Asn Thr Thr Tyr  
 165 170 175  
 Leu Trp Trp Val Asn Gly Gln Ser Leu Pro Val Ser Pro Arg Leu Gln  
 180 185 190  
 5 Leu Ser Asn Gly Asn Arg Thr Leu Thr Leu Leu Ser Val Thr Arg Asn  
 195 200 205  
 Asp Val Gly Pro Tyr Glu Cys Glu Ile Gln Asn Pro Ala Ser Ala Asn  
 210 215 220  
 Phe Ser Asp Pro Val Thr Leu Asn Val Leu Tyr Gly Pro Asp Ala Pro  
 10 225 230 235 240  
 Thr Ile Ser Pro Ser Asp Thr Tyr Tyr His Ala Gly Val Asn Leu Asn  
 245 250 255  
 Leu Ser Cys His Ala Ala Ser Asn Pro Pro Ser Gln Tyr Ser Trp Ser  
 260 265 270  
 15 Val Asn Gly Thr Phe Gln Gln Tyr Thr Gln Lys Leu Phe Ile Pro Asn  
 275 280 285  
 Ile Thr Thr Lys Asn Ser Gly Ser Tyr Ala Cys His Thr Thr Asn Ser  
 290 295 300  
 Ala Thr Gly Arg Asn Arg Thr Thr Val Arg Met Ile Thr Val Ser Asp  
 20 305 310 315 320  
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 Ser Ile Met Ile Gly Val Leu Ala Arg Val Ala Leu Ile  
 340 345

25

<210> 138

<211> 459

<212> PRT

<213> Homo sapiens

<400> 138

Met Ala Pro Leu Cys Pro Ser Pro Trp Leu Pro Leu Leu Ile Pro Ala  
5 1 5 10 15  
Pro Ala Pro Gly Leu Thr Val Gln Leu Leu Leu Ser Leu Leu Leu Leu  
20 25 30  
Met Pro Val His Pro Gln Arg Leu Pro Arg Met Gln Glu Asp Ser Pro  
35 40 45  
10 Leu Gly Gly Gly Ser Ser Gly Glu Asp Asp Pro Leu Gly Glu Glu Asp  
50 55 60  
Leu Pro Ser Glu Glu Asp Ser Pro Arg Glu Glu Asp Pro Pro Gly Glu  
65 70 75 80  
Glu Asp Leu Pro Gly Glu Glu Asp Leu Pro Gly Glu Glu Asp Leu Pro  
15 85 90 95  
Glu Val Lys Pro Lys Ser Glu Glu Glu Gly Ser Leu Lys Leu Glu Asp  
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Leu Pro Thr Val Glu Ala Pro Gly Asp Pro Gln Glu Pro Gln Asn Asn  
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20 Ala His Arg Asp Lys Glu Gly Asp Asp Gln Ser His Trp Arg Tyr Gly  
130 135 140  
Gly Asp Pro Pro Trp Pro Arg Val Ser Pro Ala Cys Ala Gly Arg Phe  
145 150 155 160  
Gln Ser Pro Val Asp Ile Arg Pro Gln Leu Ala Ala Phe Cys Pro Ala  
25 165 170 175  
Leu Arg Pro Leu Glu Leu Leu Gly Phe Gln Leu Pro Pro Leu Pro Glu  
180 185 190  
Leu Arg Leu Arg Asn Asn Gly His Ser Val Gln Leu Thr Leu Pro Pro  
195 200 205  
453

Gly Leu Glu Met Ala Leu Gly Pro Gly Arg Glu Tyr Arg Ala Leu Gln  
 210 215 220  
 Leu His Leu His Trp Gly Ala Ala Gly Arg Pro Gly Ser Glu His Thr  
 225 230 235 240  
 5 Val Glu Gly His Arg Phe Pro Ala Glu Ile His Val Val His Leu Ser  
 245 250 255  
 Thr Ala Phe Ala Arg Val Asp Glu Ala Leu Gly Arg Pro Gly Gly Leu  
 260 265 270  
 Ala Val Leu Ala Ala Phe Leu Glu Glu Gly Pro Glu Glu Asn Ser Ala  
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 Tyr Glu Gln Leu Leu Ser Arg Leu Glu Glu Ile Ala Glu Glu Gly Ser  
 290 295 300  
 Glu Thr Gln Val Pro Gly Leu Asp Ile Ser Ala Leu Leu Pro Ser Asp  
 305 310 315 320  
 15 Phe Ser Arg Tyr Phe Gln Tyr Glu Gly Ser Leu Thr Thr Pro Pro Cys  
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 Ala Gln Gly Val Ile Trp Thr Val Phe Asn Gln Thr Val Met Leu Ser  
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 Ala Lys Gln Leu His Thr Leu Ser Asp Thr Leu Trp Gly Pro Gly Asp  
 20 355 360 365  
 Ser Arg Leu Gln Leu Asn Phe Arg Ala Thr Gln Pro Leu Asn Gly Arg  
 370 375 380  
 Val Ile Glu Ala Ser Phe Pro Ala Gly Val Asp Ser Ser Pro Arg Ala  
 385 390 395 400  
 25 Ala Glu Pro Val Gln Leu Asn Ser Cys Leu Ala Ala Gly Asp Ile Leu  
 405 410 415  
 Ala Leu Val Phe Gly Leu Leu Phe Ala Val Thr Ser Val Ala Phe Leu  
 420 425 430  
 Val Gln Met Arg Arg Gln His Arg Arg Gly Thr Lys Gly Gly Val Ser  
 454

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Tyr Arg Pro Ala Glu Val Ala Glu Thr Gly Ala

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CLAIMS:

1. A method of diagnosing colon cancer in an individual comprising:
  - (a) obtaining a serum sample from said individual; and
  - 5 (b) detecting the presence of TIMP1 in said sample, wherein the presence of TIMP1 in said sample is indicative of colon cancer in said individual.
2. The method of claim 1, wherein said step of detecting comprises:
  - (a) contacting said serum sample with a polypeptide ligand which is capable of binding to TIMP1 under conditions which permit said polypeptide ligand to bind to TIMP1; and
  - 10 (b) detecting the binding of said polypeptide ligand to TIMP1, wherein detection of binding is indicative of the presence of TIMP1 in said sample.
3. The method of claim 2, wherein said polypeptide ligand is an antibody.
4. The method of claim 2 or claim 3, wherein said polypeptide ligand comprises a detectable label.
- 15 5. The method of any one of the preceding claims, wherein said individual is a human.
6. The method of any one of the preceding claims, further comprising detecting at least one other colon cancer specific marker in said sample, wherein the presence of TIMP1 and said at least one other colon cancer-specific marker is indicative of colon cancer in said individual.
7. The method of claim 6, wherein said colon cancer-specific marker is selected from the group consisting of the nucleic acid molecules of SEQ ID Nos 1, 3, 5-71, the polypeptide molecules of SEQ ID Nos 2, 4, 72-138, CA 19-9, CA 72-4, TF, sTn, Tn, CA 50, CA 549, CA 242, LASA, and Du-PAN 1 - 5.
- 20 8. The method of claim 6 or claim 7, wherein said step of detecting comprises:
  - (a) contacting said serum sample with a first polypeptide ligand which is capable of binding to TIMP1 and a second polypeptide ligand which is capable of binding to said colon cancer-specific marker, under conditions which permit said first and second polypeptide ligands to bind to TIMP1 and said colon cancer-specific marker, respectively; and
  - 25

(b) detecting the binding of said first polypeptide ligand to TIMP1 and said second polypeptide ligand to said colon cancer-specific marker, wherein detection of binding is indicative of the presence of TIMP1 and said colon cancer-specific marker in said sample.

9. The method of claim 8, wherein said first and second polypeptide ligand are each an  
5 antibody.

10. The method of claim 8 or claim 9, wherein said first and second polypeptide ligand comprises a detectable label.

11. The method of any one of claims 1 to 10, further comprising the step of detecting the presence of REG1 $\alpha$  in said sample, wherein the presence of REG1 $\alpha$  in said sample is indicative  
10 of colon cancer in said individual.

12. A method of diagnosing colon cancer in an individual comprising:

(a) obtaining a serum sample from an individual; and

(b) detecting the presence of a nucleic acid molecule which encodes TIMP1 in said sample, wherein the presence of TIMP1 of said nucleic acid molecule in said sample is indicative  
15 of colon cancer in said individual.

13. The method of claim 12, further comprising detecting at least one other nucleic acid molecule which encodes at least one other colon cancer-specific marker in said sample, wherein the presence of said nucleic acid sequence encoding TIMP1 and said nucleic acid sequence encoding said at least one other colon cancer-specific marker is indicative of colon cancer in said  
20 individual.

14. The method of claim 12 or claim 13, wherein said colon cancer specific marker is selected from the group consisting of SEQ ID Nos 1, 3, 5-71, the polypeptide molecules of SEQ ID Nos 2, 4, 72-138, CA 19-9, CA 72-4, TF, sTn, Tn, CA 50, CA 549, CA 242, LASA, and Du - PAN 1 - 5.

25 15. The method of any one of claims 12 to 14, further comprising the step of detecting presence of a nucleic acid molecule which encodes REG1 $\alpha$  in said sample, wherein the presence of REG1 $\alpha$  of said nucleic acid molecule in said sample is indicative of colon cancer in said individual.



## ABSTRACT

### DETECTION METHODS USING TIMP1

5       The present invention relates to a method for detecting the presence of colorectal cancer  
in an individual, wherein colorectal cancer is detected by detecting the presence of Reg1 $\alpha$  or  
TIMP1 nucleic acid or amino acid molecules in a clinical sample obtained from the patient,  
wherein Reg1 $\alpha$  or TIMP1 expression is indicative of the presence of colorectal cancer. The  
invention further relates to a method for detecting the presence of colorectal cancer in an  
10 individual, wherein colorectal cancer is detected by detecting the presence of Reg1 $\alpha$  or TIMP1  
nucleic acid or amino acid molecules in a clinical sample, in addition to detecting the presence of  
one or more additional colorectal cancer associated markers.

Figure 1.

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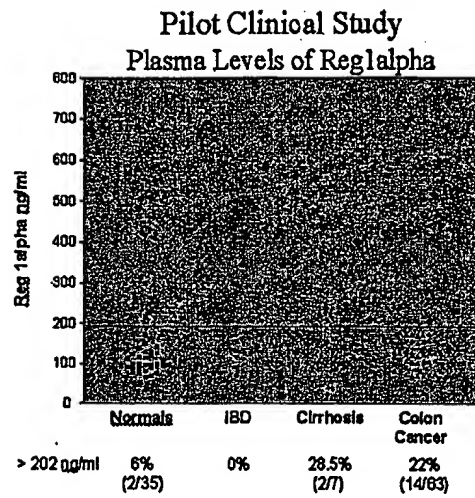




Figure 2

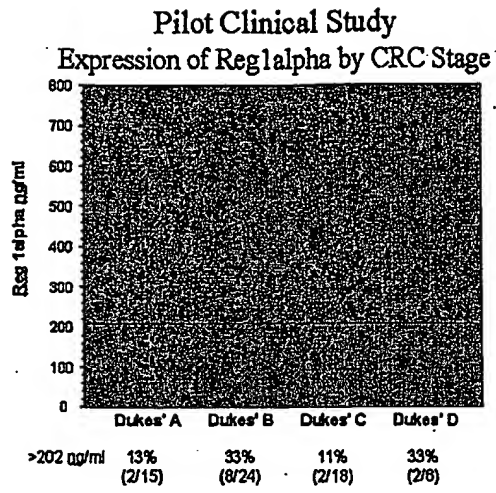
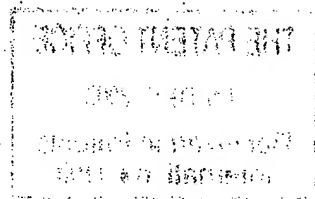
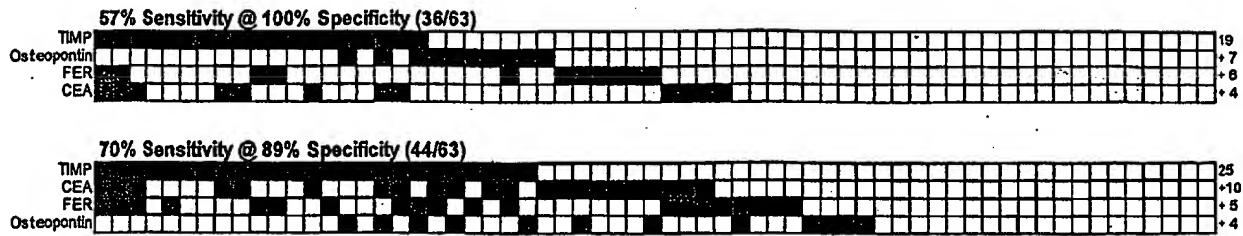


Figure 3.



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